EXHIBIT 9

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(54) Title: SYNTHESIS OF DERIVATIVES OF GINKGOLIDE C

(I)
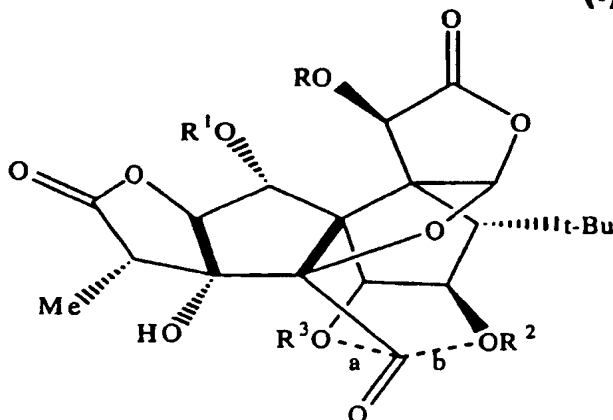
(57) Abstract: The subject invention provides ginkgolide C derivatives compounds having the structure: wherein R is H or -A-Ar, where A is an alkyl group; and Ar is an aryl group, which may contain heteroatoms and may be unsubstituted or substituted by one to five substituents each selected from the group consisting of hydrogen, alkoxy, -CH$_2$CO$_2$R^4, and - CH$_2$CONR^{5}R^6; where R^4 is an alkyl group; and R^5 and R^6 are each, independently, hydrogen or a branched or unbranched alkyl group; wherein R^1 is H or -COR^7, where R^7 is alkyl, aryl or amino; wherein R^2 is present or absent, and when present is H, COR^8 or -CO-Z-R^8; where R^8 is alkyl, aryl or amino; andZ is oxygen; wherein R^9 is present or absent, and when present is -COR^9; where R^9 is alkyl or aryl; wherein only one of R^2 or R^3 is present in the compound; wherein only two of R, R^1, R^2 and R^3 are H; and wherein each of a and b designates a single covalent bond which is present or absent, where bond a is present when R^3 is absent and bond b is present when R^2 is absent; or an optically pure enantiomer of the compound. Additionally, the subject invention provides methods of inhibiting the activity of a glycine receptor using these compounds.

Applicants: Koji Nakanashi et al.
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Filed: November 9, 2004
Exhibit 9

SYNTHESIS OF DERIVATIVES OF GINKGOLIDE C

5   This invention has been made with government support under
National Institutes of Health grant MH068817.   Accordingly,
the U.S. Government has certain rights in the invention.

Throughout   this   application   various   publications   are
10   referenced   in   parenthesis.   The   disclosures   of   these
publications in their entireties are hereby incorporated by
reference into this application in order to more fully
describe the state of the art to which this invention
pertains.
15

Background of the Invention

The *Ginkgo biloba* tree is among the oldest living plants and
is referred to as a "living fossil". It was introduced into
20   the Western world in the 18th century and admired for its
unique beauty, especially the leaves, as exemplified by a 1815
poem by Wilhelm von Goethe referring to its beauty (Goethe,
1819).   The *Ginkgo* tree has a long history of use in
traditional Chinese medicine, but it was not until the 1960's
25   that a standardized extract of *G. biloba* leaves, EGb 761, was
introduced into the European markets (Defeudis, 1998).   Today
G. biloba extract is one of the most popular botanical
medicines worldwide.

30   Numerous beneficial effects of EGb 761 has been postulated
including improving neuroprotection in Alzheimer's disease.
Alzheimer's disease is a progressive, inexorable loss of
cognitive function associated with an excessive number of

senile plaques in the cerebral cortex and subcortical gray matter, which also contains β-amyloid and neurofibrillary tangles consisting of tau protein. The cause of Alzheimer's disease is not known (Merck Manual, 1999).

5

EGb 761 has also been postulated in improving peripheral vascular function, inhibition of thrombosis and embolism cognitive disorders, anti-inflammatory and antiproliferative activities, as well as antioxidant activities (Defeudis, 10 2000). EGb 761 is a complex mixture of compounds, the main ingredients being flavonoids and terpene trilactones (ginkgolides and bilobalide) that comprise 24% and 6%, respectively, of the total extract (Ahlemeyer, 1998; Drieu, 1986). It is considered that the flavonoids act as 15 antioxidants, while the terpene trilactones are involved in anti-inflammation and prevention of blood clotting associated with the antagonistic activity at the platelet-activating factor (PAF) receptor (McKenna, 2001). However, the neuroprotective effects of EGb 761 have so far not been 20 associated with specific components of the extract (Peskind, 1998; Simonson, 1998).

The terpene trilactones, the ginkgolides (Figure 1) and bilobalide, are unique components of EGb 761, the structures 25 of which were elucidated in 1967 (Maruyama, 1967; Maruyama, 1967; Maruyama, 1967; Maruyama, 1967; Woods, 1967; Nakanishi, 1967; Okabe, 1967). The ginkgolides are diterpene trilactones with a cage-like skeleton consisting of six 5-membered rings, i.e., a spiro[4.4]nonane carbocyclic ring, three lactones, and 30 a tetrahydrofuran moiety. Terpene trilactones from G. biloba are also among the very few natural products containing a tert-butyl group.
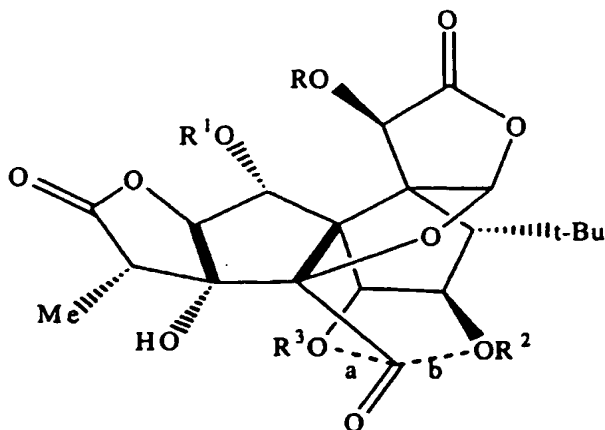
-2-

In contrast to many studies on the neuroprotective effects of EGb 761, the ginkgolides have not been extensively studied partly due to limited availability of pure ginkgolides. The finding in 1985 that ginkgolide B (GB, 2) was a potent

5   antagonist of the PAF receptor (PAFR) (Braquet, 1986; Braquet, 1985) led to extensive structure-activity relationship (SAR) studies on this receptor (Rapin, 1998; Braquet, 1987; Braquet, 1991; Hu, 2001; Hu, 2000; Hu, 2000; Corey, 1991; Park, 1993; Park, 1995; Stromgaard, 2002). However, the significance of

10 these effects in relation to the neuroprotective effects of EGb 761 is not clear (Stromgaard, 2003).

The first indication of a direct interaction of ginkgolides with important targets in the brain was discovered when

15 ginkgolides were shown to be potent and highly selective antagonists of the inhibitory glycine receptor (GlyR) (Stromgaard, 2003; Kondratskaya, 2002). The GlyR is a ligand-gated ion channel found primarily in spinal cord and brain stem, but also in higher brain regions such as hippocampus and

20 developing cortex that consists of $\alpha 1$-$\alpha 4$ and β subunits (Betz, 2001). Only a few ligands for GlyRs have been available, the classical example being the convulsant strychnine, a competitive antagonist. However, since the neuropharmacology and functional importance of GlyRs in higher brain regions is

25 not well characterized (Chattipakorn, 2002) new potent and selective ligands are needed for further investigations of the GlyR.

The introduction of combinatorial chemistry and application of

30 related techniques such as parallel or split-and-pool synthesis, solid and solution-phase strategies have opened avenues to libraries of various compounds (Marcaurelle, 2002; Arya, 2001; Ganesan, 2002; Abel, 2002; Krchnak, 2002;

-3-

Schreiber, 2000). These compounds could be entirely artificial or derivatives of natural products with possible enhanced bioactivities. Recently diversity-oriented semi-synthetic methods have been used for the preparation of

5 library of natural product derivatives for biological activity studies (Abel, 2002). In the following we describe a parallel solution-phase synthesis of a ginkgolide combinatorial library. Diversity is achieved by modification of traditional synthetic methods to prepare novel ginkgolide derivatives in a

10 selective fashion. The ginkgolide derivatives have been evaluated as antagonists of the GlyR using a fluorescence-based high-throughput screening assay.

Summary of the Invention

.The subject invention provides compounds having the structure:

wherein R is H or -A-Ar,

 where A is an alkyl group; and

 Ar is an aryl group, which may contain heteroatoms and may be unsubstituted or substituted by one to five substituents each selected from the group consisting of hydrogen, alkoxy, $-CH_2CO_2R^4$, and $-CH_2CONR^5R^6$;

  where R^4 is an alkyl group; and

  R^5 and R^6 are each, independently, hydrogen or a branched or unbranched alkyl group;

wherein R^1 is H or $-COR^7$,

 where R^7 is alkyl, aryl or amino;

wherein R^2 is present or absent, and when present is H, $-COR^8$ or $-CO-Z-R^8$;

 where R^8 is alkyl, aryl or amino; and

 Z is oxygen;

wherein R³ is present or absent, and when present is -COR⁹;

where R⁹ is alkyl or aryl;

5

wherein only one of R² or R³ is present in the compound;

wherein only two of R, R¹, R² and R³ are H; and

10   wherein each of a and b designates a single covalent bond
which is present or absent,

where bond a is present when R³ is absent and bond b
is present when R² is absent;
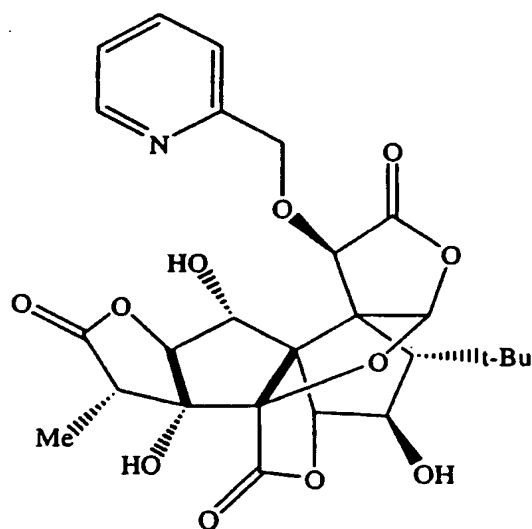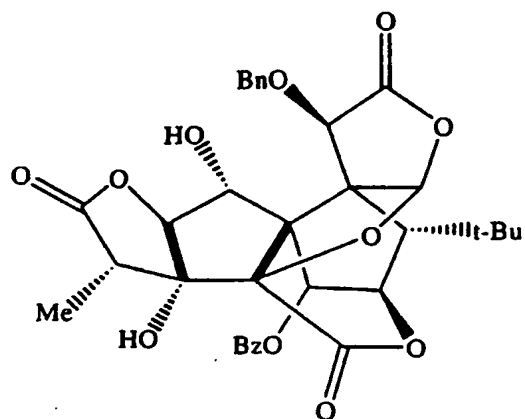
15   or an optically pure enantiomer of the compound.

The invention also provides a method of inhibiting the
activity of a glycine receptor comprising contacting the
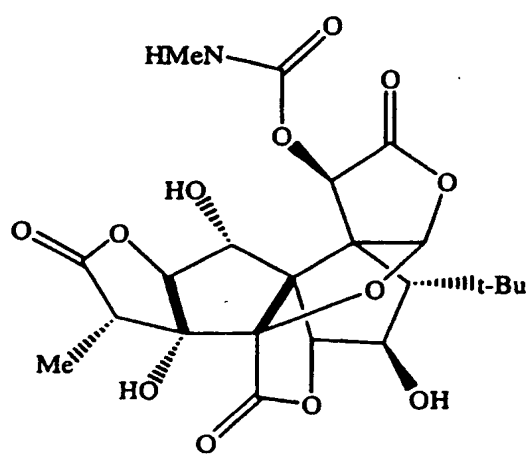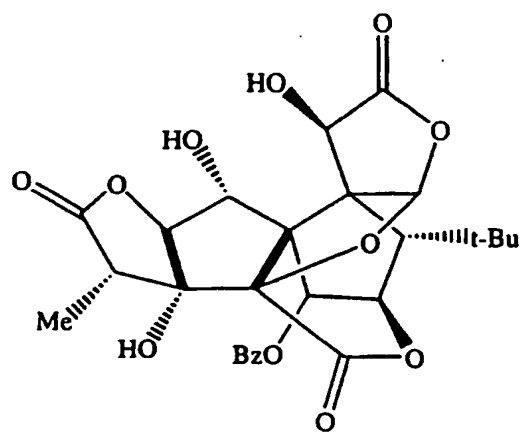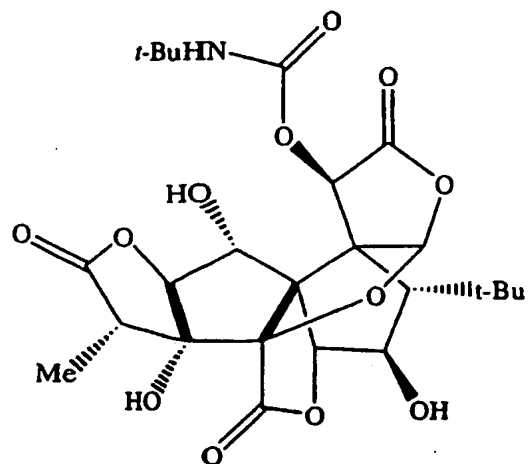glycine receptor with the compound having the structure
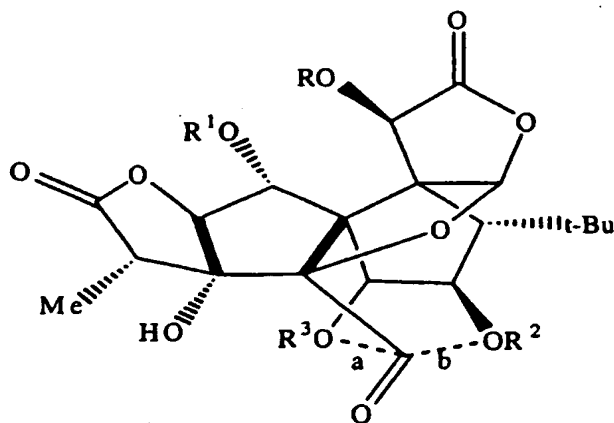
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The invention further provides a method of treating Alzheimer's disease in a subject in need of such treatment, comprising administering to the subject a compound having the structure
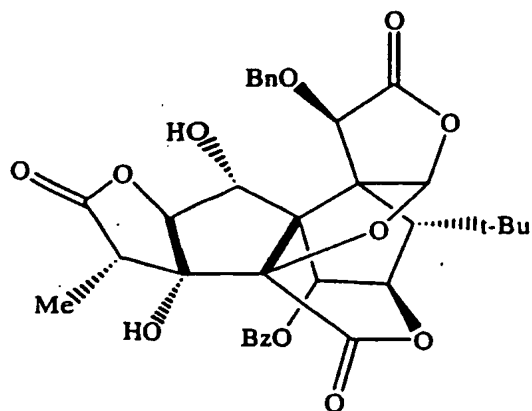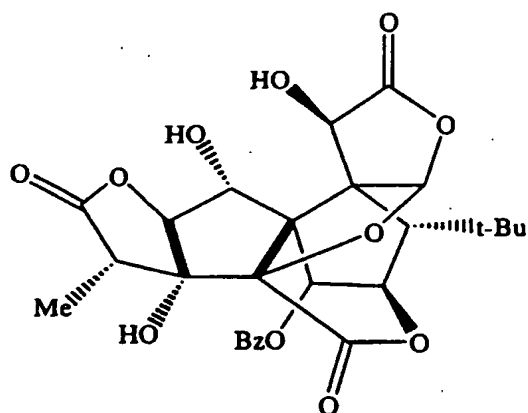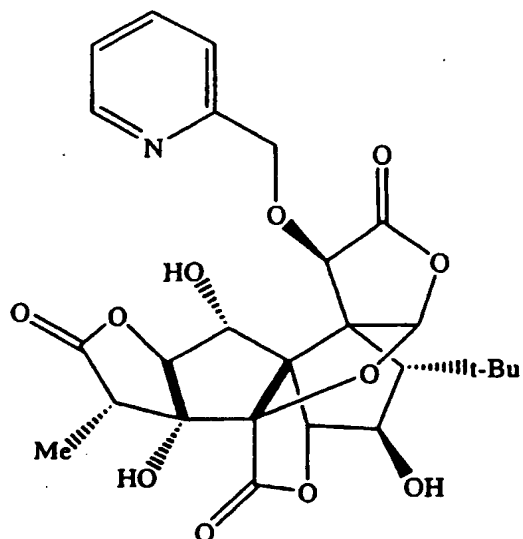
5

, or

The subject invention also provides a pharmaceutical composition comprising a compound having the structure

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, or

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The subject invention also provides a process of preparing the compound having the structure

comprising the step of reacting a compound having the structure

with an electrophile to form the above-indicated compound.

The subject invention still further provides a compound having the structure

-12-
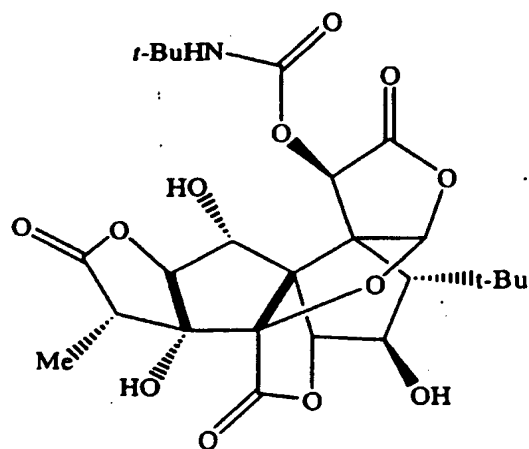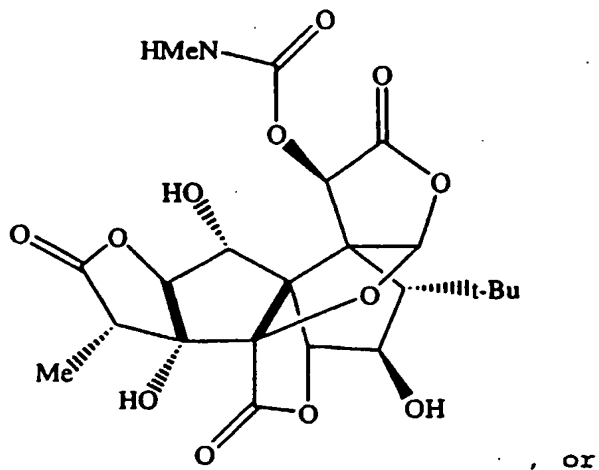
wherein Y is oxygen or -NH-.

Description of the Figures

Figure 1.   Ginkgolides A, B, C, J, and M.

5 **Figure 2.**   10-Alkyl-iso-GC-1,6-bisacetates.

Figure 3.   Benzoates of Ginkgolide C.

Detailed Description of the Invention

·The subject invention provides compounds having the structure:
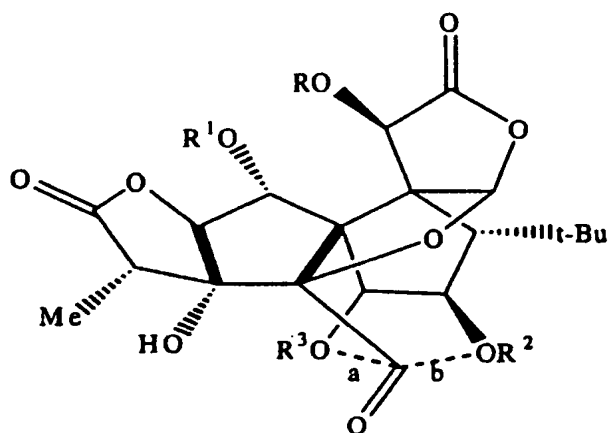
5

wherein R is H or -A-Ar,

where A is an alkyl group; and

Ar is an aryl group, which·may contain heteroatoms

10   ·and may be unsubstituted or substituted by one to

five   substituents   each   selected   from   the   group

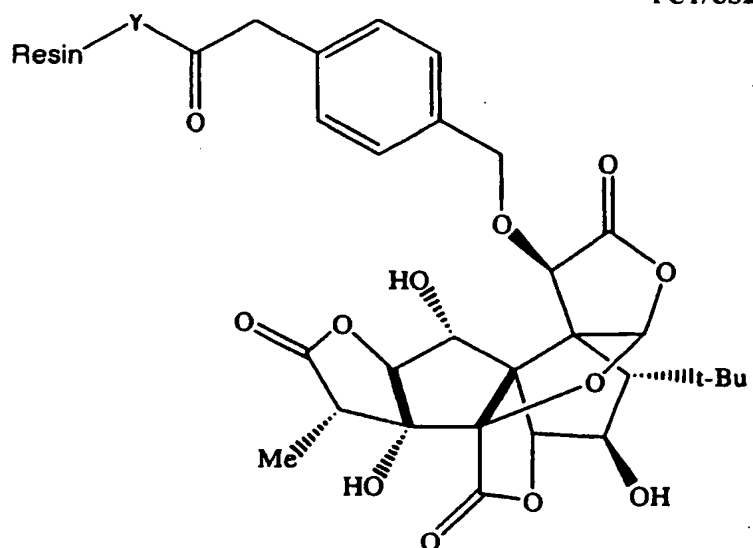consisting   of   hydrogen,   alkoxy, $-CH_2CO_2R^4$,   and   -

$CH_2CONR^5R^6$;

where R^4 is an alkyl group; and

15   R^5 and R^6 are each, independently, hydrogen or a

branched or unbranched alkyl group;

wherein R^1 is H or $-COR^7$,

where R^7 is alkyl, aryl or amino;

20

wherein R^2 is present or absent, and when present is H, -

COR^8 or $-CO-Z-R^8$;

where R^8 is alkyl, aryl or amino; and

Z is oxygen;

-15-

wherein R³ is present or absent, and when present is -COR⁹;
        where R⁹ is alkyl or aryl;

5

wherein only one of R² or R³ is present in the compound;

wherein only two of R, R¹, R² and R³ are H; and

10   wherein each of a and b designates a single covalent bond
        which is present or absent,
                where bond a is present when R³ is absent and bond b
                is present when R² is absent;

15   or an optically pure enantiomer of the compound.

    In one embodiment, the compound has the structure
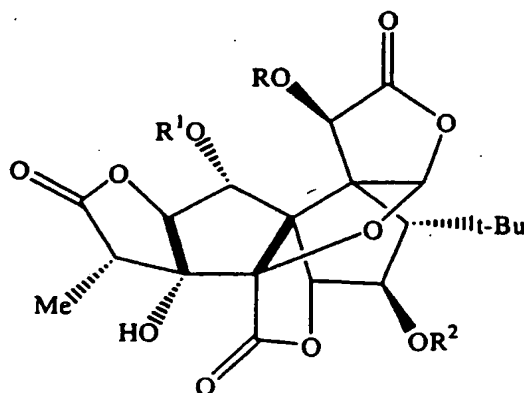
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    In another embodiment, the compound has the structure
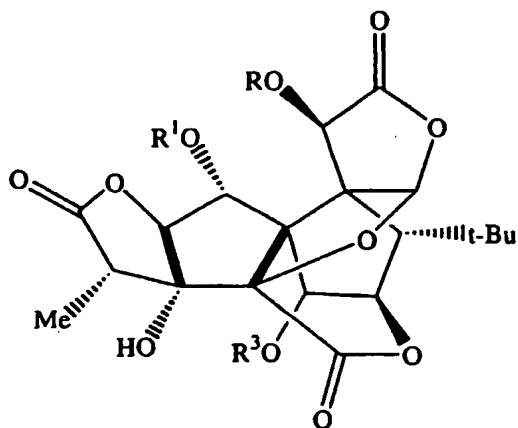
-16-

In a further embodiment, the compound has the structure

5
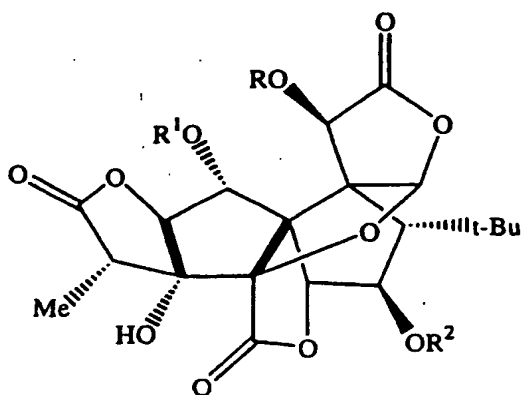
wherein R is H or -A-Ar-;

    where A is $-CH_2-$,

    Ar is a phenyl group or a picolyl group, either of
10   which may be substituted or unsubstituted by a
    substituent selected from the group consisting of
    hydrogen, methoxy, $-CH_2CO_2Me$, and $-CH_2CONH_2$;

In another embodiment, R is H, benzyl, para-methoxybenzyl or
15 picolyl.
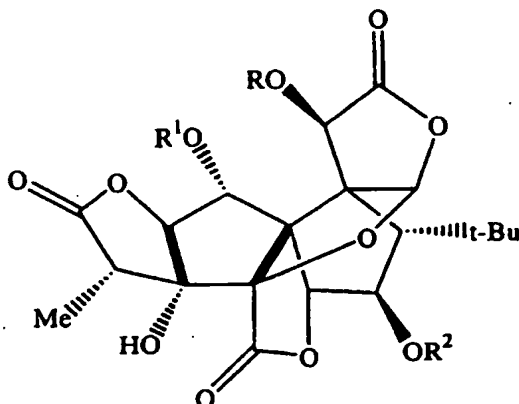
-17-

In one embodiment, the compound has the structure:

5

wherein R^1 is H or -COR^7;

where R^7 is methyl, phenyl or -NR^{5}R^6;

where R^5 and R^6 are each, independently, hydrogen,
methyl, or t-butyl, or wherein R^5 and R^6 together

10   with the nitrogen to which they are attached form a
morpholine or piperidine.

In a further embodiment, R^1 is H, benzoyl, -COMe, -CONHMe, -
CONHtBu, piperidyl, or morpholinyl.

15

In yet another embodiment, the compound has the structure

-18-

wherein R² is H, -COR⁸ or CO-Z-R⁸;

where R⁸ is -NR⁵R⁶ or phenyl, which may be
unsubstituted or substituted by one to five

5   substituents which are each, independently, halogen
or -NO₂.

where R⁵ and R⁶ are each, independently,
hydrogen, methyl, or t-butyl, or wherein R⁵ and
R⁶ together with the nitrogen to which they are

10   attached together form a morpholine or
piperidine.

In yet a further embodiment, R² is H, benzoyl, -COMe, -
CO₂C₆H₄NO₂, -CONHMe, -CONHtBu, piperidyl or morpholinyl.

15

In still another embodiment, the compound has the structure

20   wherein R is H or -A-Ar-;

where A is -CH₂-,
Ar is a phenyl group or a picolyl group, either of
which may be substituted or unsubstituted by a
substituent selected from the group consisting of

25   hydrogen, methoxy, -CH₂CO₂Me, and -CH₂CONH₂.

-19-
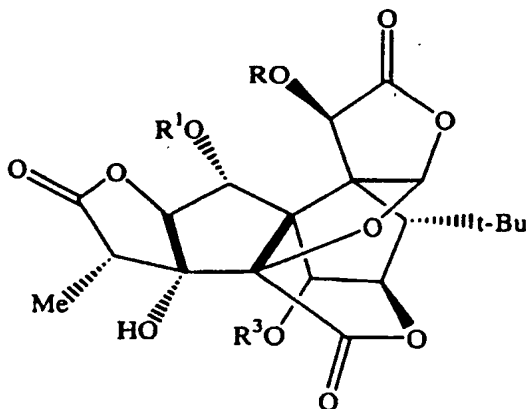
In one embodiment, R is H, benzyl, _p_-methoxybenzyl or picolyl.

In yet another embodiment, the compound has the structure

5

wherein R^1 is H or $-COR^7$,

     where R^7 is methyl, phenyl or $-NR^5R^6$;
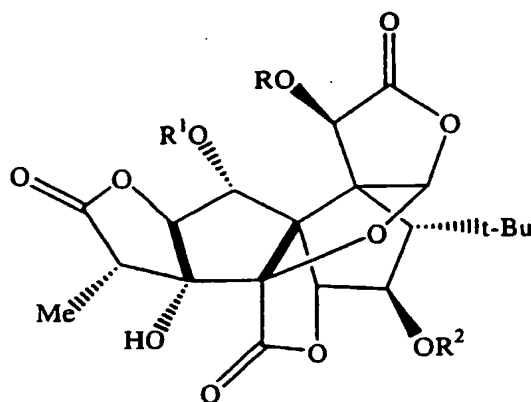
10   where R^5 and R^6 are each, independently, hydrogen, methyl, or t-butyl, or wherein R^5 and R^6 together with the nitrogen to which they are attached together form a morpholine or piperidine.

15 In a further embodiment, R^1 is H, phenyl, -COMe, -CONHMe, -CONHtBu, $-CONC_5H_{10}$ or $CONC_4H_8O$.

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In a yet further embodiment the compound has the structure
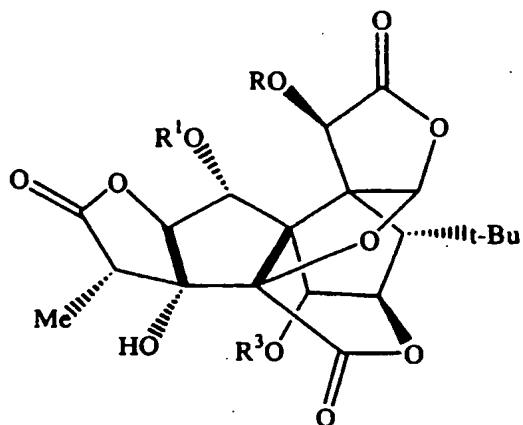
5   wherein R^3 is benzoyl, -COMe or -CO$_2$C$_6$H$_4$NO$_2$.

In another embodiment, the compound has the structure

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-21-
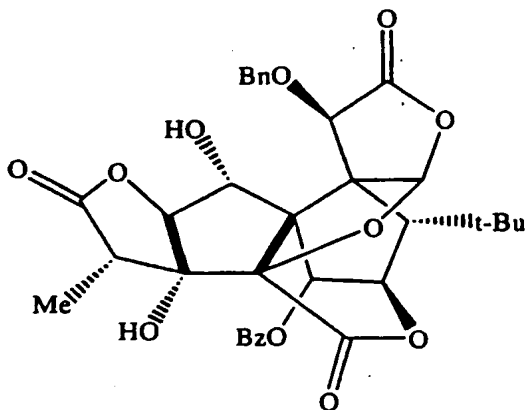
In an even yet further embodiment, the compound has the structure
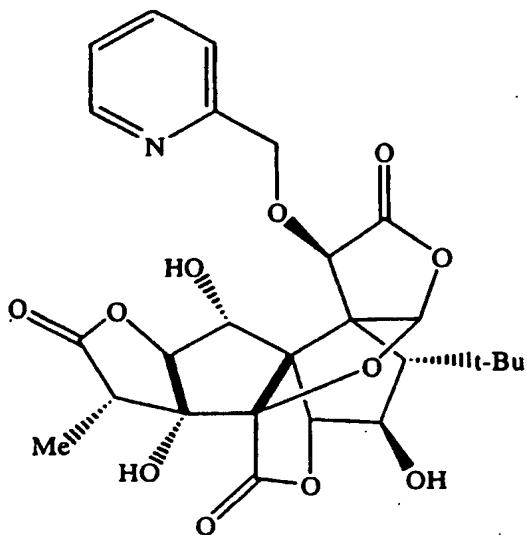
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In still yet another embodiment, the compound has the structure
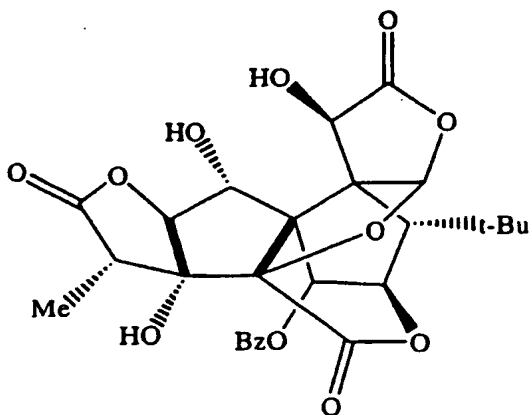
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In yet another embodiment, the compound has the structure

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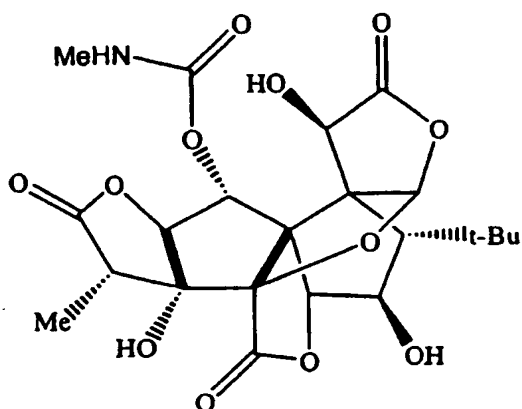
In still another embodiment, the compound has the structure
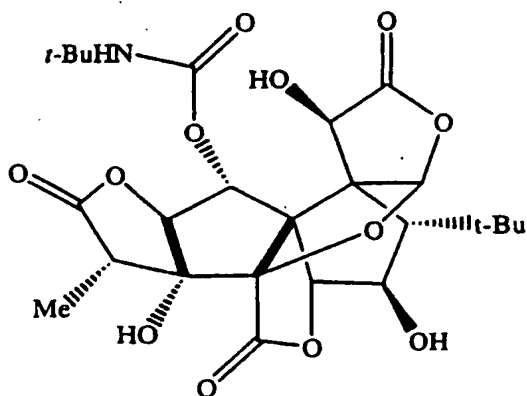
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In yet another embodiment, the compound has the structure

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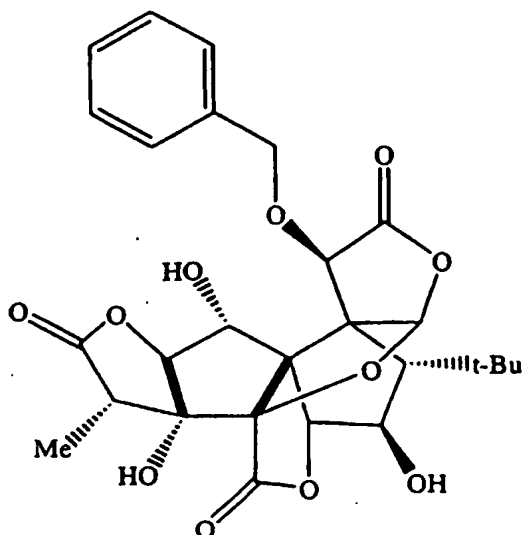
In still another embodiment, the compound has the structure
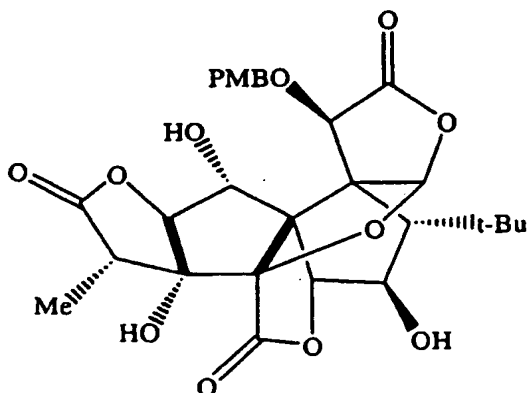
10 The invention also provides a method of inhibiting the
activity of a glycine receptor comprising contacting the
glycine receptor with the compound having the structure
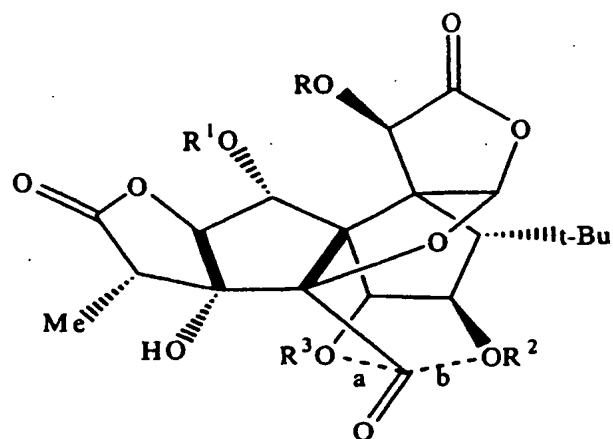
In another embodiment of the method, the compound has the structure

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, or
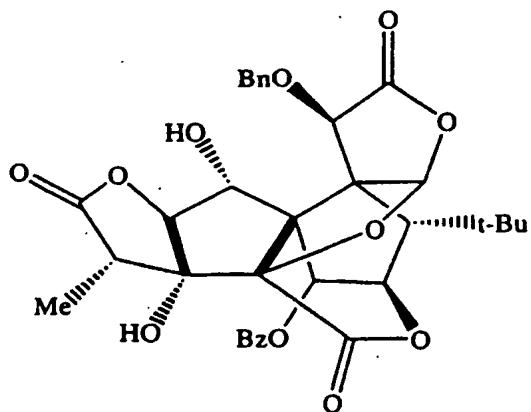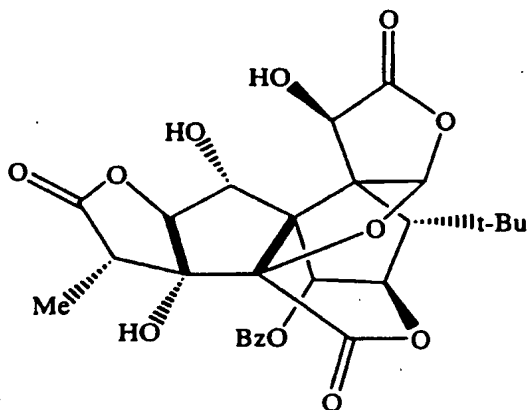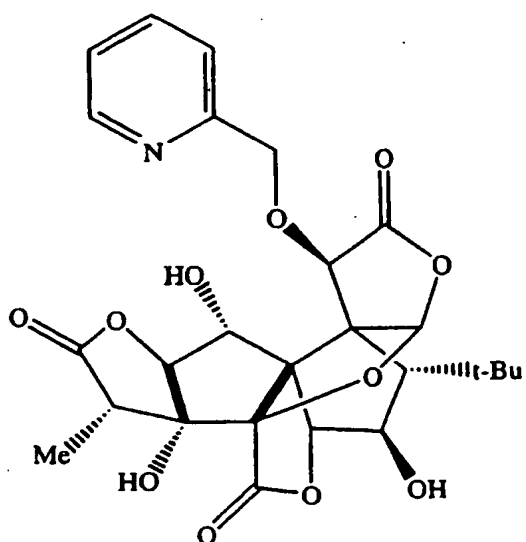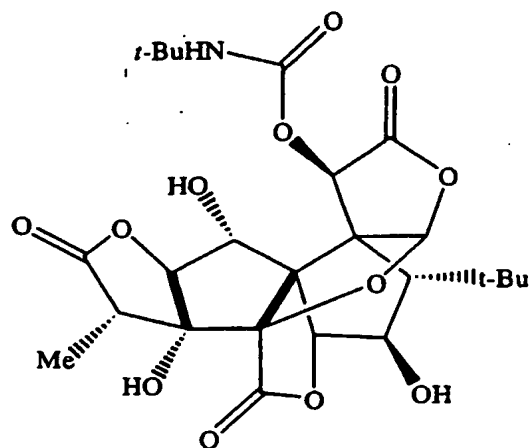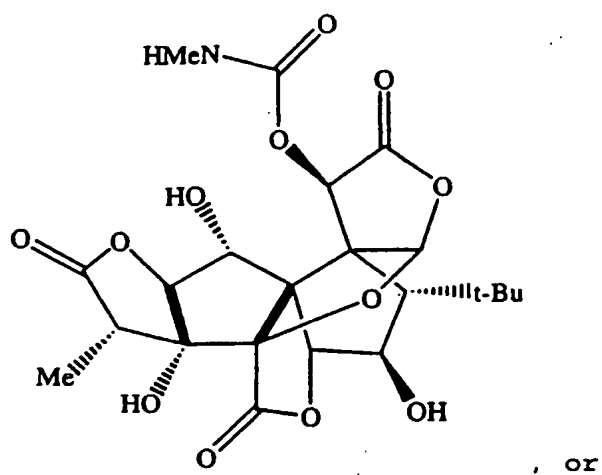
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The invention further provides a method of treating Alzheimer's disease in a subject in need of such treatment, comprising administering to the subject a compound having the
10   structure

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, or

The subject invention also provides a pharmaceutical composition comprising a compound having the structure

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, or
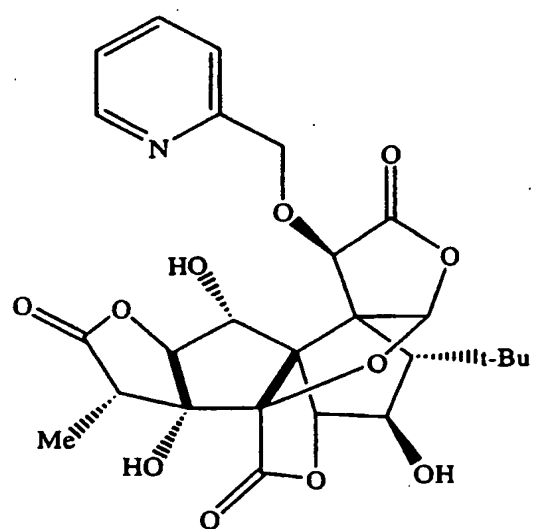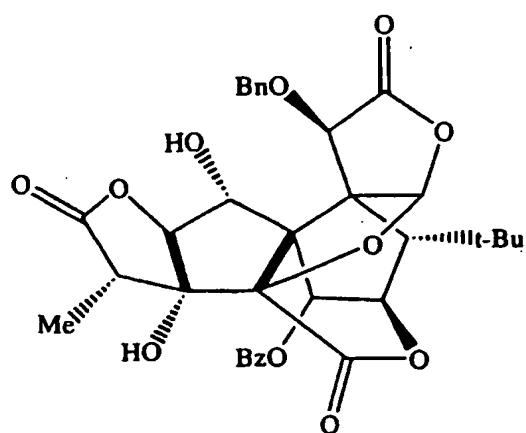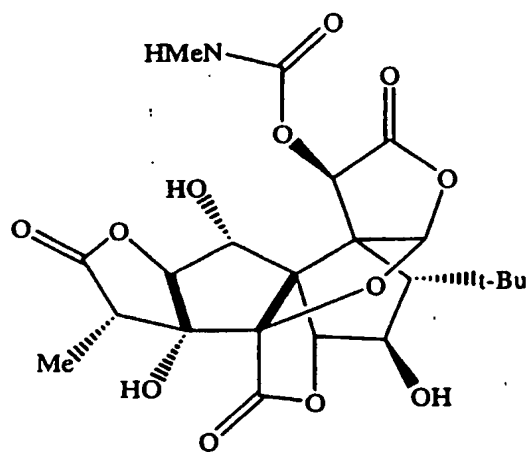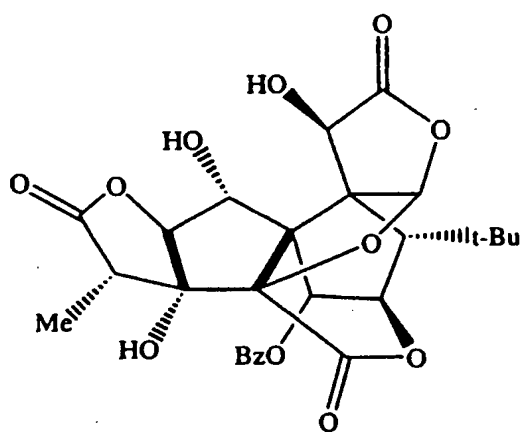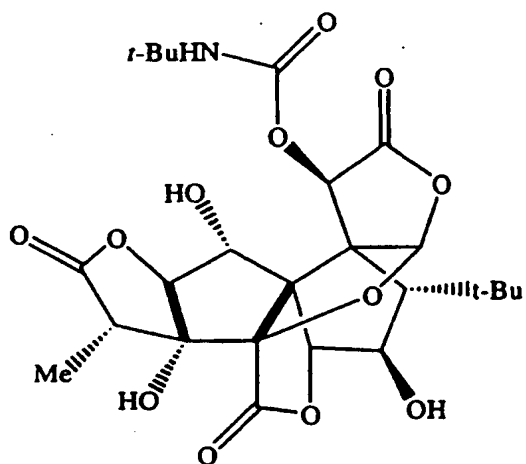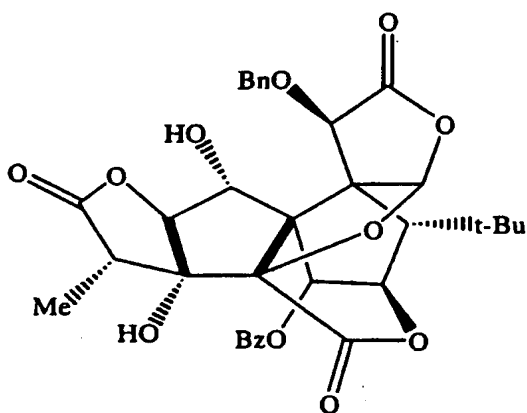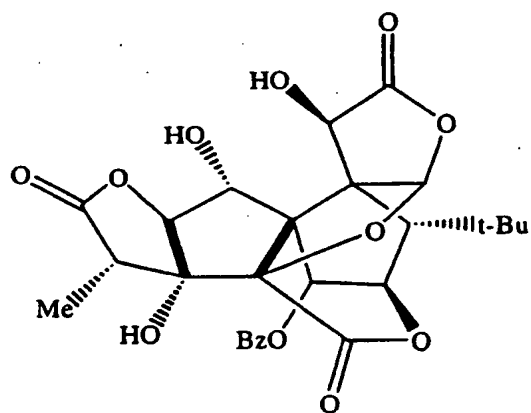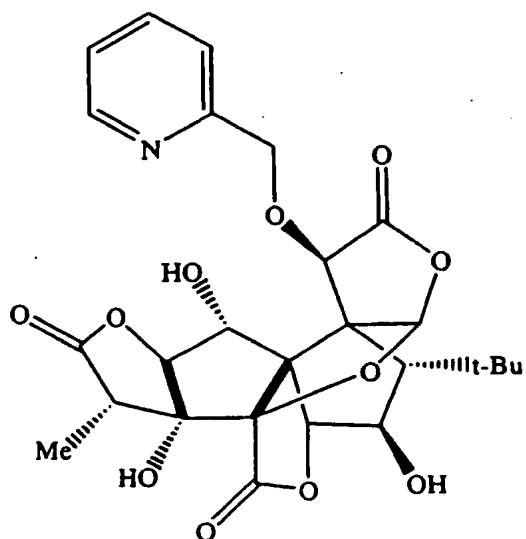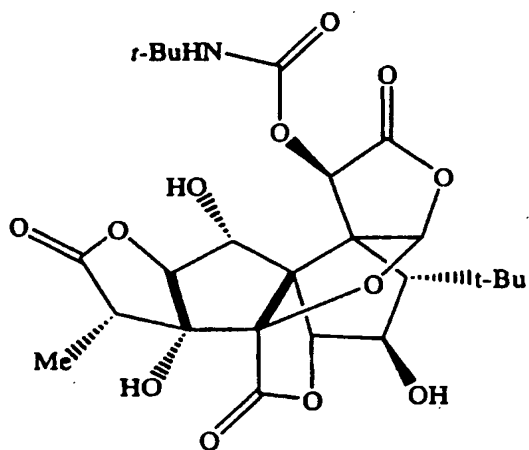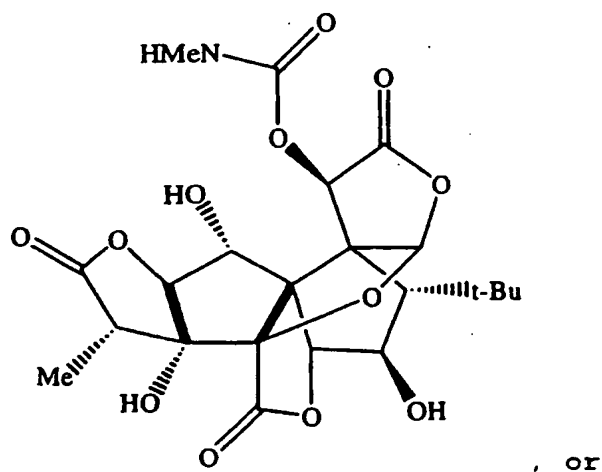
5

and a pharmaceutical carrier.

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-32-

The subject invention also provides a process of preparing the compound having the structure

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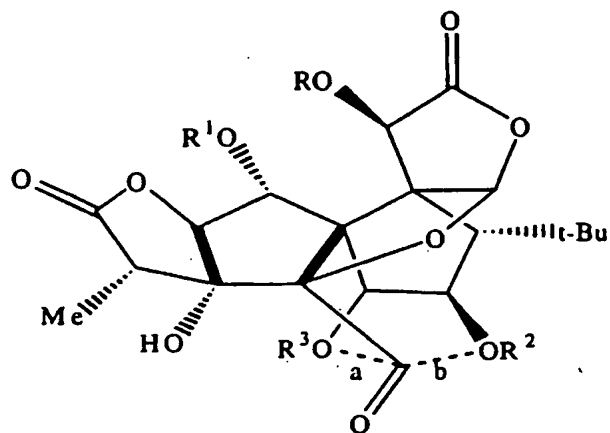
comprising the step of reacting a compound having the structure
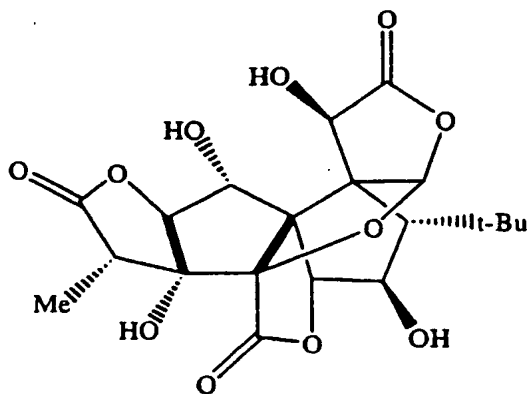
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with an electrophile to form the above-indicated compound.

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In another embodiment, the process provides the compound having the structure

comprising the steps of:

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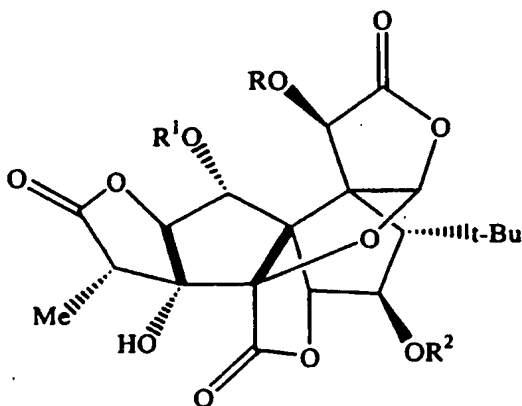
    i)   reacting a compound having the structure
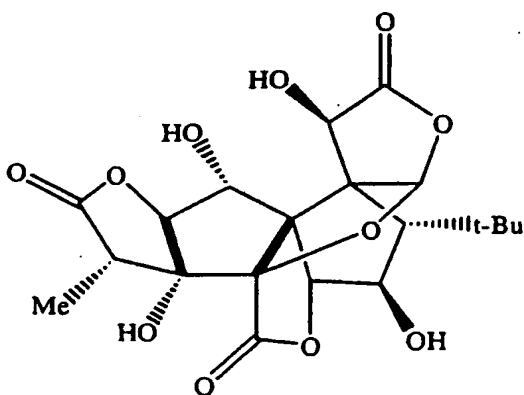
10   with either 4-methoxybenzyl chloride or benzyl chloride, and a suitable base to form a compound having the structure
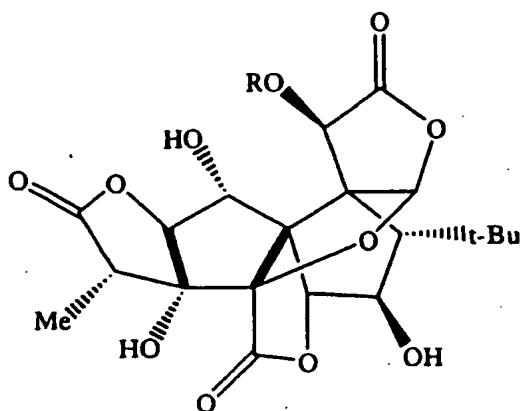
wherein R is benzyl or p-methoxybenzyl; and

5   ii) reacting the product of step i) with an electrophilic reagents to form the above-indicated compound.

The subject invention even further provides a process of
10   preparing the compound having the structure
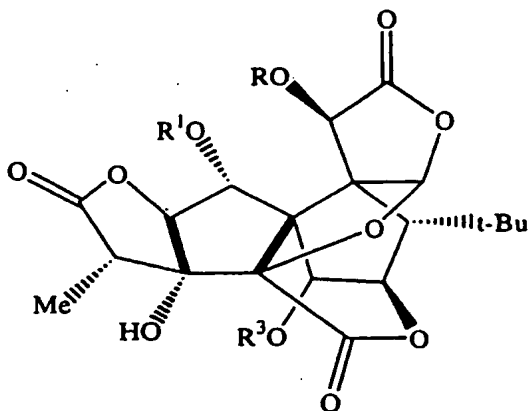
comprising the steps of:

15   i)   reacting a compound having the structure

-35-

with 4-methoxybenzyl chloride or benzyl chloride, and a
suitable base to form a compound having the structure

wherein R is benzyl or *p*-methoxybenzyl; and

ii) reacting the product of step i with the appropriate
electrophilic reagents to form the above-indicated
compound.

The subject invention still further provides a process of preparing the compound having the structure

comprising the steps of:

5

    i)   reacting a compound having the structure

10   in dimethylformamide with a resin and an appropriate base to form a compound having the structure

ii) cleaving the product of step i) from the resin by mixing the product of step i) with trifluoracetic acid in a polar solvent to form a compound having the structure
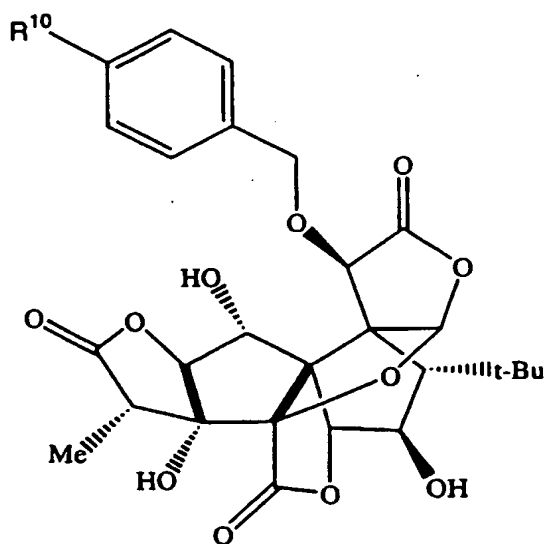
wherein R^{10} is -H, -CH$_2$CO$_2$H or CH$_2$CONH$_2$; and

iii) dissolving the product of step ii) and a suitable amine base in an appropriate solvent and reacting with benzoic anhydride, thereby forming the above-indicated compound.

5

The subject invention yet even further provides a process of preparing the compound having the structure
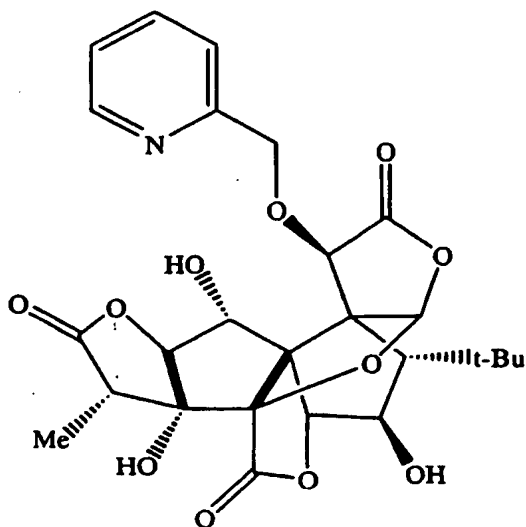
comprising the step of reacting a compound having the
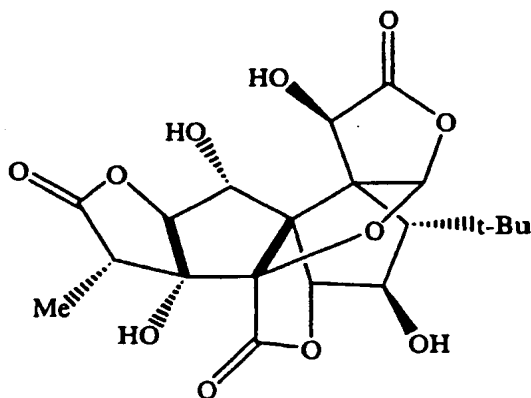
10   structure

with 2-picolyl chloride in a polar solvent with a suitable base, thereby forming the above-indicated compound.

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The subject invention provides a process of preparing the compound having the structure
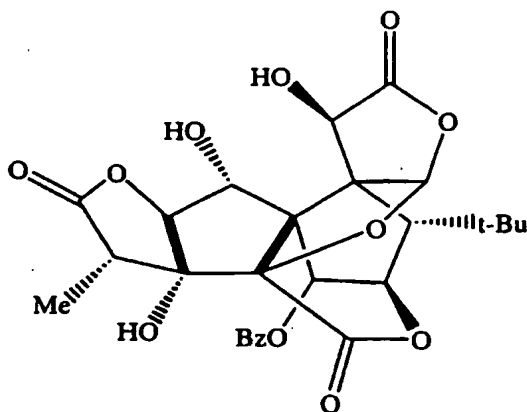
comprising the steps of:

i)   reacting a compound having the structure
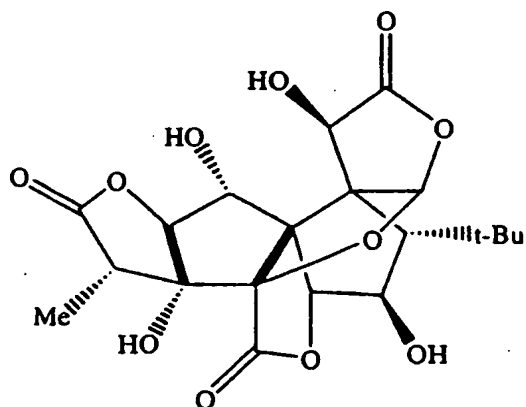
with 4-methoxybenzyl chloride in a polar solvent with a
suitable base, providing a compound having the structure

5

; and

ii) dissolving the product of step i) and a suitable
amine base in a polar solvent and reacting with benzoic
10   anhydride, thereby forming the above-indicated compound.

15

The subject invention still further provides a process of preparing the compound having the structure

5

comprising the steps of:

i)   reacting a compound having the structure

10
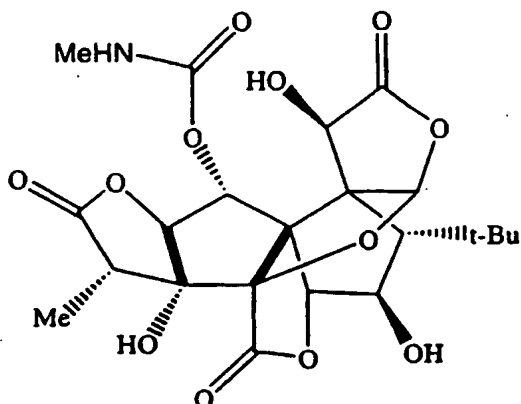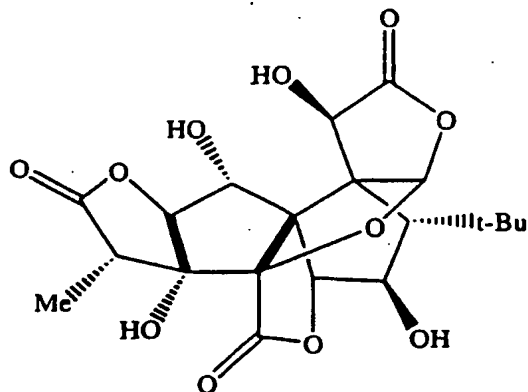
with 4-methoxybenzyl chloride in an appropriate polar solvent with a suitable base, providing a compound having the structure

15

; and

ii) dissolving the product of step i) and iPr₂EtN base in a suitable solvent and reacting with p-nitrophenyl chloroformate and then with MeNH₂, forming a compound having the structure

; and

iii) dissolving the product of step ii) in a suitable solvent and reacting with (NH₄)₂Ce(NO₃)₆, thereby forming the above-indicated compound.

The subject invention yet further provides a process of preparing the compound having the structure

comprising the steps of:

5

i)   reacting a compound having the structure

10   with 4-methoxybenzyl chloride in an a polar solvent with a suitable base, providing a compound having the structure

; and

ii) dissolving the product of step i) and *i*Pr$_2$EtN base in a suitable solvent and reacting with *p*-nitrophenyl chloroformate and then with tBuNH$_2$, thereby forming the product

; and

iii) dissolving the product of step ii) in a suitable solvent and reacting with (NH$_4$)$_2$Ce(NO$_3$)$_6$, thereby forming the above-indicated compound.

The subject invention still further provides a compound having the structure

5

wherein Y is oxygen or -NH-.

Experimental Details

10   **Materials and Methods.** All reactions were performed under argon at ambient temperature in dry solvents and yields refer to isolated products, unless otherwise stated. GC (3) originated from early structural studies (Maruyama, 1967; Maruyama, 1967; Maruyama, 1967; Maruyama, 1967; Woods, 1967),

15   and was recrystalized from ethanol/water and dried in dessicator. All other reagents were purchased and used as received. Polystyrene resin, Wang resin and bromopolystyrene resin were obtained from Advanced ChemTech, DES resin and sulfonyl chloride resin were obtained from Aldrich, Tentagel®

20   resin was purchased from Rapp-Polymere Gmbh. Reactions were monitored by analytical TLC with silica gel 60 F_{254} and spots were visualized by heating and UV light (254 nm). Flash

chromatography was performed using silica gel (230 – 400 mesh).

^{1}H-NMR and ^{13}C-NMR spectra were recorded with Bruker (300, 400 or 500 MHz) spectrometers. The chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane (in $CDCl_3$) or calibrated according to residual solvent peak as an internal standard (DMSO-d_6, δ 2.50, MeOD, δ 3.30). Assignment of peaks was achieved using 2D methods (COSY), by comparison with published data where available and comparison with ^{1}H-NMR spectra of parent ginkgolides. In certain cases, HSQC was used instead of ^{13}C-NMR. High-resolution mass spectra (HRMS) were measured on JEOL JMS-HX110/100A HF mass spectrometer under FAB conditions with NBA as the matrix. In general, all ginkgolide derivatives decomposed above 250 °C.

<u>Abbreviations</u>

Ac   = CH_3CO

Bn   = $-CH_2C_6H_5$

Bz   = $-COC_6H_5$

<u>**SYNTHESIS**</u>

Representative procedure for attachment of GC (3) to polystyrene resin with silyl linker. To a chlorodiethylsilylpolystyrene resin (100 mg, 0.052 mmol) in glass vial with PTFE septa in the stopper was added a solution of GC (3, 45.8 mg, 0.104 mmol, 2 equiv), iPr$_2$EtN (18.2 mL, 0.104 mmol, 2 equiv) and dimethylaminopyridine (DMAP, 1.3 mg, 0.01 mmol, 0.2 equiv) in THF/CH_2Cl_2 (1:1, 0.52 mL). The reaction mixture was agitated gently on a rotary shaker at ambient temperature for 24 h and then filtered and washed with CH_2Cl_2 (3 x 2 mL) and THF (3 x 2 mL) alternately, then with Et_2O (2 x 2 mL) and dried under high vacuum.

7-pipsyl-GC (6). To a suspension of GC (3, 99.8 mg, 0.227 mmol) and 4-iodobenzenesulfonyl chloride (205.7 mg, 0.680 mmol, 3 equiv) in CH_2Cl_2 (2.25 mL) was added pyridine (73 mL, 0.906 mmol, 4 equiv) and the reaction mixture was stirred for 26 h. The solvent was removed under reduced pressure, the residue dissolved in EtOAc and washed with 1M aq. HCl, brine and dried with $MgSO_4$. The crude product was purified by flash column chromatography (gradient 40-99 % EtOAc/hexanes, 1 % AcOH) to obtain 113.8 mg of pure 6 (73% yield) and 24.3 mg of recovered GC (25 %). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.18 – 8.10 (m, $2H_{AR}$), 7.78 – 7.70 (m, $2H_{AR}$), 7.57 (d, J = 5.5 Hz, 1H, 10-H), 6.52 (s, 1H, 3-OH), 6.13 (s, 1H, 12-H), 5.30 (d, J = 4.2 Hz, 1H, 1-OH), 5.16 (d, J = 4.1 Hz, 1H, 6-H), 5.01 (d, J = 5.5 Hz, 1H, 10-H), 4.85 (dd, J = 12.4, 4.1 Hz, 1H, 7-H), 4.60 (d, J = 6.5 Hz, 1H, 2-H), 4.09 (dd, J = 6.5, 4.2 Hz, 1H, 1-H), 2.80 (q, J = 7.1 Hz, 1H, 14-H), 1.95 (d, J = 12.4 Hz, 1H, 8-H), 1.10 (d, J = 7.1 Hz, 3H, 16-CH_3), 0.98 (s, 9H, tBu); ^{13}C-NMR (75 MHz, MeOD) δ 8.16, 29.24, 33.20, 43.17, 50.03, 64.78, 68.71, 70.24, 75.03, 76.67, 81.10, 84.50, 93.47, 100.06, 103.62, 111.14, 130.49, 137.04, 140.39, 171.66, 174.40, 178.05. HRMS (FAB) calcd for $C_{26}H_{28}O_{13}SI$ 707.0295, found 707.0265.

Attachment of 6 to a resin (7). To a sample tube was added TentaGel® HL-NH_2 (93 mg, 42.6 mmol), 6 (30.1 mg, 42.6 mmol, 1 equiv), Et_3N (17 mL, 0.122 mmol, 2.9 equiv), Pd(PPh$_3$)$_4$ (1 mg, 0.9 mmol, 0.02 equiv) and DMF (0.626 mL). The tube was placed into autoclave, which was purged with carbon monoxide three times before applying a pressure of 15 atm. After being left at 80 – 90°C for 14 h, the resin was transferred into a plastic syringe with porous PE plug and consecutively washed with DMF (3 x 3 mL), CH_2Cl_2 (2 x 3 mL), DMF (2 x 3 mL), acetonitrile (2 x 3 mL), acetonitrile/H_2O (1:1, 4 x 3 mL), MeOH

(3 x 3 mL), CH$_2$Cl$_2$ (3 x 3 mL), and Et$_2$O (3 x 3 mL) and dried under vacuum to obtain **7**.

Attachment of 4-(bromomethyl)phenylacetic acid to a Wang resin

5   **(8)**. To a solution of 4-(bromomethyl)phenylacetic acid (185.7 mg, 0.811 mmol, 8 equiv) in THF (1.6 mL) was added DIC (127 mL, 0.811 mmol, 8 equiv) and mixture was agitated for 5 min until white crystals developed. More THF (1.6 mL) was added to redissolve the precipitate and the solution was mixed with

10 Wang resin (169 mg, 0.101 mmol, 1 equiv). The reaction mixture was gently agitated on a rotary shaker for 9 h and then filtered, washed with THF (4 x 5 mL) and CH$_2$Cl$_2$ (4 x 5 mL) alternately, then with CH$_2$Cl$_2$ (2 x 5 mL), MeOH (2 x 5 mL) and dried under vacuum to obtain **8**.

15

Attachment of 4-(bromomethyl)phenylacetic acid to a Rink-amide resin (9). To a solution of 4-(bromomethyl)phenylacetic acid (47.4 mg, 0.207 mmol, 8 equiv) in THF (0.4 mL) was added 2-dimethylaminoisopropyl chloride hydrochloride (DIC, 32.4 mL,

20 0.207 mmol, 8 equiv) and mixture was agitated for 5 min until white crystals developed. More THF (0.6 mL) was added to re-dissolve the precipitate and the solution was mixed with Rink-amide TentaGel$^{®}$ resin (108 mg, 0.026 mmol, 1 equiv). The reaction mixture was gently agitated on a rotary shaker for

25 2.5 h and then filtered, washed with THF (4 x 3 mL) and CH$_2$Cl$_2$ (4 x 3 mL) alternately, then with CH$_2$Cl$_2$ (2 x 3 mL), Et$_2$O (2 x 3 mL) and dried under vacuum to obtain **9**.

Synthesis of silicon-linked solid-phase anchored benzyl

30 **bromide (14)**. To a solution of 4-(allyldimethylsilyl)benzyl alcohol (475 mg, 2.30 mmol) in THF (4.6 mL) at 0 °C was slowly added 9-borabicyclo[3.3.1]nonane (9-BBN, 9.2 mL, 0.5M in THF, 4.6 mmol, 2 equiv). The reaction mixture was warmed up slowly to room temperature and then stirred for 10 h. To the mixture

was then added bromopolystyrene (1.075 g, 1.5 mmol/g, 1.61 mmol, 0.7 equiv), K_2CO_3 (2.3 mL, 3M in H_2O, 6.9 mmol, 3 equiv), DMF (6.3 mL) and finally $Pd(PPh_3)_4$ (53.3 mg, 0.046 mmol, 0.02 equiv). The resulting suspension was slowly stirred in closed

5   vial at 70-75 °C for 24 h. $Pd(PPh_3)_4$ (53.3 mg, 0.046 mmol, 0.02 equiv) was added to the reaction mixture, which was again reacted at 70-75 °C for additional 24 h. The resin was filtered and washed with DMF (3 x), H_2O (3 x), DMF (3 x), then with CH_2Cl_2 (3 x) and MeOH (3 x) alternately and with MeOH (1 x) and

10   dried under high vacuum to obtain 1.265 g of dry resin. The resin ($\leq$1.61 mmol) was placed into solid-phase reactor and PPh_3 (846 mg, 3.22 mmol, 2 equiv), CBr_4 (1.070 g, 3.22 mmol, 2 equiv) and CH_2Cl_2 (16 mL) were added at 0 °C. The mixture was agitated on rotary shaker at room temperature for 6 h and then

15   filtered and washed with CH_2Cl_2 (3 x), then MeOH (2 x) and CH_2Cl_2 (2 x) alternately and then with MeOH (2 x) and dried under vacuum to obtain 1.371 g of resin 14. Loading of the resin was determined by cleavage with Br_2 to obtain 4-bromobenzyl bromide (1.17 mmol/g, 85% yield from

20   bromopolystyrene).

General procedure for attachment of GC (3) to solid-phase anchored benzyl bromide (10, 11, 15). To a mixture of a resin (8, 9, or 14) (0.1 mmol), GC (3) (79.2 mg, 0.18 mmol, 1.8

25   equiv) and finely grounded K_2CO_3 (41.5 mg, 0.3 mmol, 3 equiv) in a plastic syringe with porous PE plug was added DMF and the suspension was gently agitated on rotary shaker for 30 h. The resin was filtered and washed with DMF (3 x) for GC (3) recovery and the resin was further washed with H_2O (3 x), DMF

30   (3 x), then CH_2Cl_2 (3 x) and MeOH (3 x) alternately and dried under high vacuum. A test for the presence of alkyl halides (using 4-nitrobezylpyridine) was negative (Kuisle, 1999).

Cleavage from Wang resin (12). To a sample of resin 10 (12 mg) in a vial was added TFA/CH_2Cl_2 (1:1, 0.2 mL). After standing for 30 min, resin was filtered and washed with TFA/CH_2Cl_2 (2:3, 0.17 mL), TFA/CH_2Cl_2 (1:3, 0.22 mL), and TFA/CH_2Cl_2 (1:4, 0.2

5   mL). Combined washing solutions were mixed with filtrate and volatiles were removed under reduced pressure. Residue ·was dissolved in MeOH (0.1 mL) and treated with CH_2N_2 (1 mL, ~0.2M in Et_2O) for 10 min. Volatiles were removed under reduced pressure to provide **12** (~90% purity based on ^1H NMR). ^1H-NMR

10   (400 MHz, $CDCl_3$) δ 7.40 − 7.30 (m, 4H$_{AR}$), 5.99 (s, 1H, 12-H), 5.48 (d, J = 9.3 Hz, 1H, benzyl), 5.13 (d, J = 4.4 Hz, 1H, 6-H), 4.93 (s, 1H, 10-H), 4.61 (d, J = 9.3 Hz, 1H, benzyl), 4.53 (d, J = 7.8 Hz, 1H, 2-H), 4.22 (dd, J = 3.3, 7.8 Hz, 1H, 1-H), 4.18 − 4.08 (m, 1H, 7-H), 3.71 (s, 3H, -OCH_3), 3.66 (s, 2H,

15   CH_2), 3.05 (q, J = 7.0 Hz, 1H, 14-H), 2.82 (d, J = 3.4 Hz, 1H, 1-OH), 2.73 (bs, 1H, 3-OH), 2.11 (d, J = 11.5 Hz, 1H, 7-OH), 1.69 (d, J = 12.4 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.23 (s, 9H, tBu) ; HRMS (FAB) calcd for $C_{30}H_{35}O_{13}$ 603.2078, found 603.2081.

20

Cleavage from Rink-amide resin (13). To a sample of resin 11 (27.6 mg) in a vial was added TFA/H_2O (9:1, 0.4 mL). After standing for 50 min, the resin was filtered and washed with TFA/H_2O (9:1, 2 x 0.28 mL). The combined washing solutions were

25   mixed with filtrate and volatiles were removed under reduced pressure to provide **13** (95% purity based on ^1H NMR). ^1H-NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 1H, NH$_A$H$_B$), 7.35 − 7.28 (m, 2H$_{AR}$), 7.28 − 7.21 (m, 2H$_{AR}$), 6.89 (s, 1H, NH$_A$H$_B$), 6.48 (s, 1H, 3-OH), 6.19 (s, 1H, 12-H), 5.65 (bs, 1H, 7-OH), 5.34 (d, J = 10.9 Hz,

30   1H, benzyl), 5.22 (s, 1H, 10-H), 4.94 (d, J = 4.1 Hz, 1H, 6-H), 4.80 (d, J = 4.0 Hz, 1H, 1-OH), 4.63 (d, J = 10.9 Hz, 1H, benzyl), 4.59 (d, J = 6.5 Hz, 1H, 2-H), 4.13 (dd, J = 4.0, 6.4 Hz, 1H, 1-H), 3.97 (dd, J = 4.1, 12.5 Hz, 1H, 7-H), 3.37 (s, 2H, CH_2), 2.84 (q, J = 7.1 Hz, 1H, 14-H), 1.55 (d, J = 12.5 Hz,

1H, 8-H), 1.14 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.09 (s, 9H, tBu); HRMS (FAB) calcd for C$_{29}$H$_{34}$O$_{12}$N 588.2081, found 588.2083.

Cleavage from silicone-linker resin (16). To a sample of resin 15 (12.6 mg) in a vial was added TFA/CH$_2$Cl$_2$ (1:1, 0.5 mL). After standing for 24 h, resin was filtered and washed with TFA/CH$_2$Cl$_2$ (1:1, 2 x 0.3 mL). Combined washing solutions were mixed with filtrate and volatiles were removed under reduced pressure to provide 16 (85% purity based on ^{1}H NMR). Analytical data as previously described (Vogensen, 2003).

10-Benzyloxy-GC (16). Synthesis and analytical data as previously described (Vogensen, 2003).

10-Benzyloxy-isoGC-6-benzoate (17). To a solution of 16 (18.0 mg, 0.034 mmol) in CH$_2$Cl$_2$ (0.87 mL) and iPr$_2$EtN (0.145 mL, 0.829 mmol, 24 equiv) was added benzoic anhydride (23 mg, 0.102 mmol, 3 equiv). The mixture was stirred for 11 h and then quenched with phosphate buffer (pH ~ 2 - 3, 1 mL) washed with brine and dried with MgSO$_4$. The crude product was purified by flash chromatography (30-50% EtOAc/hexanes) to obtain 17 as a white powder (16.6 mg, 77%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.15 - 8.09 (m, 2H$_{AR}$), 7.66 - 7.56 (m, 1H$_{AR}$), 7.52-7.38 (m, 7H$_{AR}$), 5.75 (s, 1H, 12-H), 5.48 (d, J =9.5 Hz, 1H, benzyl), 5.44 (d, J = 4.0 Hz, 1H, 6-H), 5.17 (s, 1H, 10-H), 5.06 (d, J =3.9 Hz, 1H, 7-H), 4.91 (d, J = 7.7 Hz, 1H, 2-H), 4.83 (d, J = 9.5 Hz, 1H, benzyl), 4.28 (dd, J = 7.6, 2.3 Hz, 1H, 1-H), 3.83 (s, 1H, 3-OH), 3.22 (q, J = 6.9 Hz, 1H, 14-H), 3.22 (d, J = 2.7 Hz, 1H, 1-OH), 2.30 (s, 1H, 8-H), 1.35 (d, J = 7.07 Hz, 3H, 16-CH$_3$), 1.25 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 6.99, 29.71, 33.74, 41.47, 61.78, 62.86, 67.73, 69.90, 73.11, 74.29, 75.21, 78.81, 84.07, 91.96, 95.53, 110.02, 127.82, 128.80, 129.23, 129.46, 129.90, 130.19, 133.65, 134.18, 165.09,

166.56, 170.70, 176.38; HRMS (FAB) calcd for $C_{34}H_{35}O_{12}$ 635.2129, found 635.2097.

10-Benzyloxy-isoGC-1,6-bisacetate (19). To a solution of **16** (8.5 mg, 0.016 mmol) in CH_2Cl_2 (0.15 mL) and iPr_2EtN (28 mL, 0.16 mmol, 10 equiv) was added acetic anhydride (15 mL, 0.16 mmol, 10 equiv). The mixture was stirred for 12 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40 – 50% EtOAc/hexanes) to obtain **19** as a white powder (8.0 mg, 81%). ^1H-NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, $5H_{AR}$), 5.66 (d, J = 3.7 Hz, 1H, 1-H), 5.63 (s, 1H, 12-H), 5.51 (d, J = 4.1 Hz, 1H, 6-H), 5.30 (d, J = 10.6 Hz, 1H, benzyl), 5.01 (s, 1H, 10-H), 4.83 (d, J = 4.1 Hz, 1H, 7-H), 4.72 (d, J = 10.6 Hz, 1H, benzyl), 4.48 (d, J = 3.7 Hz, 1H, 2-H), 3.31 (q, J = 7.5 Hz, 1H, 14-H), 3.30 (s, 1H, 3-OH), 2.20 (s, 1H, 8-H), 2.12 (s, 3H, CH_3 – acetyl), 1.31 (d, J = 7.5 Hz, 3H, $16-CH_3$), 1.30 (s, 3H, CH_3 – acetyl), 1.19 (s, 9H, tBu); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 9.56, 19.52, 20.59, 29.26, 33.63, 41.21, 61.55, 63.67, 67.20, 70.13, 73.29, 74.25, 74.98, 78.99, 84.47, 92.04, 97.31, 108.60, 128.76 (2 C), 128.93, 135.22, 166.51, 167.87, 168.74, 170.07, 175.87; HRMS (FAB) calcd for $C_{31}H_{35}O_{13}$ 615.2078, found 615.2083.

10-(4-Methoxy-benzyloxy)-isoGC-1,6-bisacetate (20). To a solution of **24** (13.4 mg, 0.024 mmol) in CH_2Cl_2 (0.24 mL) and iPr_2EtN (42 mL, 0.24 mmol, 10 equiv) was added acetic anhydride (23 mL, 0.24 mmol, 10 equiv). The mixture was stirred for 12 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40 – 70% EtOAc/hexanes) to obtain **20** as a white powder (12.1 mg, 79%). ^1H-NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, $2H_{AR}$), 6.93 – 6.86 (m, $2H_{AR}$), 5.64 (d, J = 3.8 Hz, 1H, 1-H), 5.63 (s, 1H, 12-H), 5.45 (d, J = 4.1 Hz,

1H, 6-H), 5.18 (d, *J* = 10.4 Hz, 1H, benzyl), 5.00 (s, 1H, 10-H), 4.82 (d, *J* = 4.1 Hz, 1H, 7-H), 4.69 (d, *J* = 10.4 Hz, 1H, benzyl), 4.50 (d, *J* = 3.8 Hz, 1H, 2-H), 3.81 (s, 3H, -OMe), 3.34 (s, 1H, 3-OH), 3.30 (q, *J* = 7.5 Hz, 1H, 14-H), 2.20 (s,

5   1H, 8-H), 2.12 (s, 3H, CH_3 – acetyl), 1.39 (s, 3H, CH_3 – acetyl), 1.30 (d, *J* = 7.5 Hz, 3H, 16-CH_3), 1.17 (s, 9H, *t*Bu); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.40, 19.62, 20.53, 29.27, 33.52, 41.08, 55.17, 61.28, 63.41, 66.87, 69.90, 72.62, 73.84, 74.18, 78.70, 84.15, 91.75, 96.83, 108.29, 113.65, 126.79, 130.36,

10 159.46, 165.97, 167.33, 168.21, 169.65, 175.34; HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{32}H_{36}O_{14}$ 644.2105, found 644.2082.

10-Benzyloxy-GC-7-benzoate (21). To a solution of **16** (22.9

15 mg, 0.043 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.15 mL, 1.85 mmol, 43 equiv) was added benzoyl chloride (25 mL, 0.216 mmol, 5 equiv). The mixture was stirred for 5 h and then quenched with aq. HCl (1 mL, 1M), washed with brine and dried with $MgSO_4$. The crude product was purified by flash chromatography

20 (30-40% EtOAc/hexanes) to obtain **21** as a white powder (21.6 mg, 79%). ^1H-NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H_{AR}), 7.68 – 7.58 (m, 1H_{AR}), 7.53 – 7.40 (m, 7H_{AR}), 6.08 (s, 1H, 12-H), 5.50 (dd, *J* = 12.9, 4.3 Hz, 1H, 7-H), 5.48 (d, *J* = 9.4 Hz, 1H, benzyl), 5.41 (d, *J* = 4.3 Hz, 1H, 6-H), 5.02 (s, 1H, 10-H),

25 4.76 (d, *J* = 9.4 Hz, 1H, benzyl), 4.51 (d, *J* = 7.9 Hz, 1H, 2-H), 4.26 (dd, *J* = 7.9, 3.2 Hz, 1H, 1-H), 3.07 (q, *J* = 7.0 Hz, 1H, 14-H), 2.86 (d, *J* = 3.2 Hz, 1H, 1-OH), 2.9 – 2.7 (bs, 1H, 3-OH), 2.25 (d, *J* = 12.9 Hz, 1H, 8-H), 1.31 (d, *J* = 7.0 Hz, 3H, 16-CH_3), 1.20 (s, 9H, *t*Bu); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 7.26,

30 29.36, 32.13, 41.57, 48.60, 64.03, 67.83, 73.93, 74.01, 74.15, 75.39, 76.88, 83.41, 90.53, 98.34, 109.86, 128.60, 128.74, 128.80, 129.57, 129.85, 130.06, 133.95, 134.12, 164.84, 170.50, 170.97, 175.13; HRMS (FAB) calcd for $C_{34}H_{35}O_{12}$ 635.2129, found 635.2156.

10-Benzyloxy-isoGC-1,6-bisbenzoate (22). To a solution of **16** (9.3 mg, 0.015 mmol) in CH_2Cl_2 (0.38 mL) and iPr$_2$EtN (63 mL, 0.36 mmol, 24 equiv) was added benzoic anhydride (19.9 mg,
5 0.090 mmol, 6 equiv). The mixture was stirred for 20 h and then quenched with aq. HCl (1 mL, 1M), washed with brine and dried with MgSO$_4$. The crude product was purified by flash chromatography (30-50% EtOAc / 1 % AcOH / hexanes) to obtain **22** as a white powder (7.1 mg, 64%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ
10 8.25 – 8.18 (m, 2H$_{AR}$), 7.66 – 7.58 (m, 3H$_{AR}$), 7.52 – 7.37 (m, 3H$_{AR}$), 7.21 – 7.13 (m, 2H$_{AR}$), 7.11 – 7.03 (m, 2H$_{AR}$), 7.02 – 6.95 (m, 3H$_{AR}$), 6.02 (d, J = 5.1 Hz, 1H, 1-H), 5.79 (d, J = 4.0 Hz, 1H, 6-H), 5.69 (s, 1H, 12-H), 5.03 (d, J = 4.0 Hz, 1H, 7-H), 5.01 (s, 1H, 10-H), 4.88 (d, J = 5.1 Hz, 1H, 2-H), 4.86 (s,
15 2H, benzyl), 3.66 (s, 1H, 3-OH), 3.41 (q, J = 7.3 Hz, 1H, 14-H), 2.25 (s, 1H, 8-H), 1.39 (d, J = 7.3 Hz, 3H, 16-CH$_3$), 1.08 (s, 9H, tBu); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 8.60, 29.21, 33.73, 41.42, 61.61, 64.01, 67.11, 71.02, 72.94, 73.78, 74.05, 79.05, 84.72, 92.51, 96.69, 109.00, 127.96, 128.25, 128.29, 128.62,
20 128.91, 128.98, 129.22, 129.58, 130.21, 133.08, 133.92, 134.37, 163.78, 165.61, 166.74, 170.05, 175.91; HRMS (FAB) calcd for $C_{41}H_{39}O_{13}$ 739.2391, found 739.2381.

10-Benzyloxy-GC-1-benzoate (23). To a solution of **17** (15.6
25 mg, 0.025 mmol) in DMF (0.40 mL) was added iPr$_2$EtN (50 mL, 0.29 mmol, 12 equiv) and mixture was stirred for 1.5 h at 100°C. Solvent was removed under reduced pressure, a residue was treated with phosphate buffer (pH 2 – 3, 1 mL), then extracted with EtOAc (3 x) and combined organic layers were dried with
30 MgSO$_4$. The crude product was purified by flash chromatography (30 – 50 % EtOAc/hexanes) to obtain **23** as a white solid (12.2 mg, 78%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.64 – 7.59 (m, 2H$_{AR}$), 7.51 – 7.45 (m, 1H$_{AR}$), 7.31 – 7.25 (m, 2H$_{AR}$), 6.98 – 6.91 (m, 2H$_{AR}$), 6.88 – 6.83 (m, 3H$_{AR}$), 6.03 (s, 1H, 12-H), 5.89 (d, J = 6.1 Hz,

1H, 1-H), 5.46 (d, J = 4.4 Hz, 1H, 6-H), 5.17 (d, J = 11.0 Hz,
1H, benzyl), 4.85 (s, 1H, 10-H), 4.70 (d, J = 6.1 Hz, 1H, 2-
H), 4.56 (d, J = 10.9 Hz, 1H, benzyl), 4.42 - 4.33 (m, 1H, 7-
H), 3.28 (q, J = 7.2 Hz, 1H, 14-H), 3.4 - 2.9 (bs, 1H, 3-OH),
5   2.65 - 2.3 (bs, 1H, 7-OH), 1.76 (d, J = 12.3 Hz, 1H, 8-H),
1.33 (d, J = 7.2 Hz, 3H, 16-CH$_3$), 1.15 (s, 9H, tBu); ^{13}C-NMR
(100 MHz, CDCl$_3$) δ 7.94, 29.13, 32.34, 41.20, 50.57, 65.09,
66.47, 73.55, 74.30, 75.25, 75.64, 80.32, 84.27, 92.14, 99.62,
109.34, 128.02, 128.11, 128.24, 128.34, 128.70, 129.56,
10   133.23, 134.66, 163.47, 170.25, 170.70, 174.91; HRMS (FAB)
calcd for C$_{34}$H$_{35}$O$_{12}$ 635.2129, found 635.2148.

10-(4-Methoxy-benzyloxy)-GC (24). To a solution of GC (3)
(201 mg, 0.456 mmol) in DMF (2.28 mL) was added powdered K$_2$CO$_3$
15   (315 mg, 2.28 mmol, 5 equiv) and 4-methoxybenzyl chloride (620
mL, 4.56 mmol, 10 equiv). The mixture was stirred at 60 °C for
3 h and then stirred at room temperature for 5 h. The solution
was concentrated under reduced pressure, an aq. phosphate
buffer (pH 2 - 3, 10 mL) was added and the resulting solution
20   was extracted with EtOAc (3 x) and dried with MgSO$_4$. The crude
product was purified by flash chromatography (40-100%
EtOAc/hexanes) to obtain **24** as a white powder (240 mg, 94%).
^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.35 - 7.27 (m, 2H$_{AR}$), 6.99 - 6.89 (m,
2H$_{AR}$), 5.98 (s, 1H, 12-H), 5.41 (d, J = 9.2 Hz, 1H, benzyl),
25   5.12 (d, J = 4.4 Hz, 1H, 6-H), 4.92 (s, 1H, 10-H), 4.57 (d, J
= 9.2 Hz, 1H, benzyl), 4.52 (d, J = 7.9 Hz, 1H, 2-H), 4.21
(dd, J = 3.4, 7.9 Hz, 1H, 1-H), 4.13 (m, 1H, 7-H), 3.83 (s,
3H, -OCH$_3$), 3.05 (q, J = 7.1 Hz, 1H, 14-H), 2.88 (d, J = 3.4
Hz, 1H, 1-OH), 2.75 (s, 1H, 3-OH), 2.12 (d, J = 11.5 Hz, 1H,
30   7-OH), 1.69 (d, J = 12.4 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz,
3H, 16-CH$_3$), 1.23 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.23,
29.08, 32.19, 41.65, 50.38, 55.31, 64.03, 67.08, 73.79, 75.31,
75.59, 79.33, 83.47, 90.70, 98.49, 110.13, 114.73, 126.36,

130.65, 160.56, 170.90, 171.03, 175.83; HRMS (FAB) calcd for C$_{28}$H$_{32}$O$_{12}$ 560.1894, found 560.1866.

10-(2-Pyridinyl-methoxy)-GC **(25)**. A mixture of 2-picolylchloride hydrochloride (401.4 mg, 2.45 mmol, 6 equiv) and EtOAc was washed with sat. aq. NaHCO$_3$ (2 x), brine and dried with MgSO$_4$. After filtration and removal of EtOAc, free 2-picolyl chloride was added to a solution of GC (**3**, 179.6 mg, 0.408 mmol, 1 equiv) in DMF (2.04 mL) and powdered K$_2$CO$_3$ (338 mg, 2.45 mmol, 6 equiv) was added. The mixture was briefly heated to about 60 °C and then stirred at room temperature for 15 h. The solution was concentrated under reduced pressure, an aq. phosphate buffer (pH 2-3, 10 mL) was added and resulting solution was extracted with EtOAc (3 x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (50-100% EtOAc/hexanes) to obtain **25** as a white powder (211.2 mg, 97%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.54 (d, J = 4.9 Hz, 1H$_{AR}$), 8.20 (d, J = 4.1 Hz, 1H, 1-OH), 7.79 – 7.71 (m, 1H$_{AR}$), 7.35 – 7.28 (m, 1H$_{AR}$), 7.19 – 7.11 (m, 1H$_{AR}$), 6.00 (s, 1H, 12-H), 5.67 (d, J = 13.0 Hz, 1H, benzyl), 5.43 (d, J = 4.3 Hz, 1H, 6-H), 4.96 (s, 1H, 10-H), 4.82 (d, J = 13.0 Hz, 1H, benzyl), 4.66 (d, J = 7.6 Hz, 1H, 2-H), 4.47 – 4.38 (m, 1H, 1-H), 4.27 – 4.17 (m, 1H, 7-H), 3.10 (s, 1H, 3-OH), 3.08 (q, J = 7.0 Hz, 1H, 14-H), 2.32 (d, J = 11.3 Hz, 1H, 7-OH), 1.73 (d, J = 12.4 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.18 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.33, 29.12, 32.27, 41.74, 50.55, 64.70, 67.62, 70.67, 73.81, 74.89, 75.36, 80.14, 83.06, 92.61, 98.74, 109.99, 120.37, 123.29, 137.41, 148.74, 154.52, 170.96, 171.45, 175.79; HRMS (FAB) calcd for C$_{26}$H$_{30}$O$_{11}$N 532.1819, found 532.1844.

10-(4-Methoxy-benzyloxy)-GC-7-benzoate **(26)**. To a solution of **24** (11.3 mg, 0.0202 mmol) in CH$_2$Cl$_2$ (0.34 mL) and pyridine (56 mL, 0.69 mmol, 34 equiv) was added benzoyl chloride (11.7 mL,

0.101 mmol, 5 equiv). Mixture was stirred for 7 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 - 50% EtOAc/hexanes) to obtain **26** as a

5   white powder (12.3 mg, 92%). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.13 - 8.03 (m, 2H$_{AR}$), 7.69 - 7.58 (m, 1H$_{AR}$), 7.54 - 7.44 (m, 2H$_{AR}$), 7.44 - 7.34 (m, 2H$_{AR}$), 7.03 - 6.94 (m, 2H$_{AR}$), 6.07 (s, 1H, 12-H), 5.48 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 5.40 (d, J = 9.3 Hz, 1H, benzyl), 5.40 (d, J = 4.3 Hz, 1H, 6-H), 4.99 (s, 1H, 10-

10   H), 4.70 (d, J = 9.3 Hz, 1H, benzyl), 4.50 (d, J = 7.9 Hz, 1H, 2-H), 4.25 (dd, J = 7.9, 3.4 Hz, 1H, 1-H), 3.84 (s, 3H, -OMe), 3.06 (q, J = 7.0 Hz, 1H, 14-H), 2.92 (d, J = 3.4 Hz, 1H, 1-OH), 2.90 (s, 1H, 3-OH), 2.24 (d, J = 12.8 Hz, 1H, 8-H), 1.31 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.20 (s, 9H, tBu); ^{13}C-NMR (75

15   MHz, CDCl$_3$) δ 7.28, 29.34, 32.10, 41.61, 48.57, 55.33, 64.01, 67.81, 73.70, 73.94, 73.97, 75.05, 76.84, 83.41, 90.54, 98.31, 109.87, 114.82, 126.18, 128.59, 128.73, 130.05, 130.57, 133.94, 160.61, 164.84, 170.65, 171.00, 175.28; HRMS (FAB) calcd for C$_{35}$H$_{36}$O$_{13}$ 664.2156, found 664.2129.

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10-(4-Methoxy-benzyloxy)-isoGC-6-benzoate (27). To a solution of **24** (24.6 mg, 0.0438 mmol) in CH$_2$Cl$_2$ (0.83 mL) and iPr$_2$EtN (46 mL, 0.263 mmol, 6 equiv) was added benzoic anhydride (29.7 mg, 0.131 mmol, 3 equiv). Mixture was stirred for 11 h and

25   then quenched with phosphate buffer (pH ~ 2 - 3, 1 mL), extracted with EtOAc and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 - 50% EtOAc / 1% AcOH / hexanes) to obtain **27** as a white powder (16.5 mg, 57%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.15 - 8.08 (m, 2H$_{AR}$), 7.62 - 7.55 (m,

30   1H$_{AR}$), 7.48 -7.39 (m, 2H$_{AR}$), 7.38 - 7.30 (m, 2H$_{AR}$), 6.96 - 6.88 (m, 2H$_{AR}$), 5.74 (s, 1H, 12-H), 5.42 (d, J = 4.0 Hz, 1H, 6-H), 5.40 (d, J = 9.4 Hz, 1H, benzyl), 5.16 (s, 1H, 10-H), 5.06 (d, J = 4.0 Hz, 1H, 7-H), 4.91 (d, J = 7.7 Hz, 1H, 2-H), 4.76 (d, J = 9.4 Hz, 1H, benzyl), 4.27 (dd, J = 7.7, 2.6 Hz, 1H, 1-H),

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3.84 (s, 1H, 3-OH), 3.79 (s, 3H, -OMe), 3.30 (d, J = 2.7 Hz, 1H, 1-OH), 3.22 (q, J = 7.1 Hz, 1H, 14-H), 2.30 (s, 1H, 8-H), 1.35 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.25 (s, 9H, tBu); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 6.99, 29.39, 33.76, 41.49, 55.31, 61.79, 62.91, 67.76, 69.96, 73.12, 73.86, 74.94, 78.86, 84.11, 91.98, 95.51, 110.06, 114.76, 125.78, 127.88, 128.80, 130.23, 130.98, 134.17, 160.71, 165.11, 166.61, 170.84, 176.40; HRMS (FAB) calcd for C$_{35}$H$_{36}$O$_{13}$ 664.2156, found 664.2165.

10-(4-Methoxy-benzyloxy)-GC-1-benzoate (28). To a solution of 27 (9.9 mg, 0.015 mmol) in DMF (0.25 mL) was added iPr$_2$EtN (30 mL, 0.17 mmol, 12 equiv) and the mixture was stirred for 3 h at 100°C. Solvent was removed under reduced pressure, a residue was treated with phosphate buffer (pH ~ 2 - 3, 1 mL), then extracted with EtOAc (3x) and combined organic layers were dried with MgSO$_4$. The crude product was purified by flash chromatography (30 - 50 % EtOAc/hexanes) to obtain 28 as a white solid (7.9 mg, 80%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.64 - 7.58 (m, 2H$_{AR}$), 7.52 - 7.45 (m, 1H$_{AR}$), 7.32 - 7.25 (m, 2H$_{AR}$), 6.91 - 6.85 (m, 2H$_{AR}$), 6.39 - 6.33 (m, 2H$_{AR}$), 6.02 (s, 1H, 12-H), 5.84 (d, J = 6.2 Hz, 1H, 1-H), 5.44 (d, J = 4.4 Hz, 1H, 6-H), 5.10 (d, J = 10.5 Hz, 1H, benzyl), 4.83 (s, 1H, 10-H), 4.68 (d, J = 6.2 Hz, 1H, 2-H), 4.47 (d, J = 10.5 Hz, 1H, benzyl), 4.42 - 4.33 (m, 1H, 7-H), 3.60 (s, 3H, -OMe), 3.28 (q, J = 7.1 Hz, 1H, 14-H), 3.09 (s, 1H, 3-OH), 2.37 (d, J = 12.0 Hz, 1H, 7-OH), 1.74 (d, J = 12.3 Hz, 1H, 8-H), 1.33 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.18 (s, 9H, tBu); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 7.85, 29.17, 32.34, 41.17, 50.65, 54.81, 65.09, 66.39, 73.31, 74.24, 74.99, 75.62, 80.32, 84.25, 92.11, 99.43, 109.33, 113.44, 126.84, 128.18, 128.71, 129.57, 129.88, 133.01, 159.24, 163.43, 170.31, 170.67, 174.72; HRMS (FAB) calcd for C$_{35}$H$_{36}$O$_{13}$ 664.2156, found 664.2170.

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10-(2-Pyridinyl-methoxy)-GC-7-benzoate (29). To a solution of
25 (13.2 mg, 0.0248 mmol) in CH_2Cl_2 (0.52 mL) and pyridine (87
mL, 1.08 mmol, 43 equiv) was added benzoyl chloride (14.4 mL,
0.124 mmol, 5 equiv). Mixture was stirred for 7 h and then
5   quenched with phosphate buffer (pH ~ 2 - 3, 1 mL), extracted
with EtOAc (3x) and dried with $MgSO_4$. The crude product was
purified by flash chromatography (40 - 50% EtOAc/hexanes) to
obtain **29** as a white powder (13.4 mg, 85%). ^1H-NMR (400 MHz,
$CDCl_3$) δ 8.58 (d, J = 5.0 Hz, 1H, 6-py), 8.42 (bs, 1H, 1-OH),
10 8.08 - 8.00 (m, $2H_{AR}$), 7.79 - 7.71 (m, 1H, 4-py), 7.65 - 7.56
(m, $1H_{AR}$), 7.51 - 7.42 (m, $2H_{AR}$), 7.35 - 7.28 (m, 1H, 5-py),
7.15 (d, J = 7.9 Hz, 1H, 3-py), 6.08 (s, 1H, 12-H), 5.75 (d, J
= 4.4 Hz, 1H, 6-H), 5.68 (d, J = 13.1 Hz, 1H, benzyl), 5.48
(dd, J = 12.8, 4.4 Hz, 1H, 7-H), 5.03 (s, 1H, 10-H), 4.89 (d,
15 J = 13.1 Hz, 1H, benzyl), 4.64 (d, J = 7.5 Hz, 1H, 2-H), 4.48
(bd, J = 7.5 Hz, 1H, 1-H), 3.09 (q, J = 7.0 Hz, 1H, 14-H),
2.88 (bs, 1H, 3-OH), 2.28 (d, J = 12.8 Hz, 1H, 8-H), 1.31 (d,
J = 7.0 Hz, 3H, 16-CH_3), 1.18 (s, 9H, tBu); ^{13}C-NMR (100 MHz,
$CDCl_3$) δ 7.34, 29.39, 32.24, 41.76, 48.89, 64.61, 68.43, 70.65,
20 73.84, 74.35, 74.93, 77.53, 83.04, 92.62, 98.68, 109.94,
120.22, 123.28, 128.67, 128.84, 130.00, 133.78, 137.37,
148.85, 154.47, 164.87, 170.71, 171.53, 175.63; HRMS (FAB)
calcd for $C_{33}H_{34}O_{12}N$ 636.2081, found 636.2058.

25 **GC-7-benzoate (30).** To a solution of **26** (8.0 mg, 12.0 mmol)
in acetonitrile (150 mL) and $CHCl_3$ (49 mL) was added aq.
solution of $(NH_4)_2Ce(NO_3)_6$ (14.7 mL, 24 mmol, 2 equiv, 1.63M).
The mixture was stirred for 14 h, volatiles were removed under
reduced pressure and residue was purified by flash
30 chromatography (30 - 100% EtOAc / 1% AcOH / hexanes) to obtain
30 as a white powder (4.4 mg, 68%). ^1H-NMR (400 MHz, CD_3OD) δ
8.11 - 8.05 (m, $2H_{AR}$), 7.70 - 7.62 (m, $1H_{AR}$), 7.57 - 7.49 (m,
$2H_{AR}$), 6.20 (s, 1H, 12-H), 5.54 - 5.46 (m, 2H, 6-H & 7-H), 5.19
(s, 1H, 10-H), 4.57 (d, J = 7.6 Hz, 1H, 2-H), 4.22 (d, J = 7.6

Hz, 1H, 1-H), 3.02 (q, J = 7.1 Hz, 1H, 14-H), 2.29 – 2.22 (m, 1H, 8-H), 1.23 (d, J = 7.1 Hz, 3H, 16-CH_3), 1.18 (s, 9H, tBu); HSQC correlation data in the Supporting Information ; HRMS (FAB) calcd for $C_{27}H_{28}O_{12}Na$ 567.1478, found 567.1472.

IsoGC-6-benzoate (31). To a solution of **27** (3.3 mg, 5.0 mmol) in acetonitrile (63 mL) and $CHCl_3$ (20 mL) was added aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.2 mL, 10 mmol, 2 equiv, 1.63M). The mixture was stirred for 3 h, volatiles were removed under reduced pressure and residue was purified by flash chromatography (30 – 70% EtOAc / 1% AcOH / hexanes) to obtain **31** as a white powder (2.2 mg, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.11 (m, 2H_{AR}), 7.63 – 7.55 (m, 1H_{AR}), 7.48 –7.40 (m, 2H_{AR}), 5.75 (s, 1H, 12-H), 5.64 (d, J = 3.9 Hz, 1H, 6-H), 5.30 (s, 1H, 10-H), 5.06 (d, J = 3.9 Hz, 1H, 7-H), 5.00 (d, J = 7.7 Hz, 1H, 2-H), 4.26 (d, J = 7.7 Hz, 1H, 1-H), 3.78 (s, 1H, 3-OH), 3.40 (q, J = 7.1 Hz, 1H, 14-H), 2.29 (s, 1H, 8-H), 1.37 (d, J = 7.1 Hz, 3H, 16-CH_3), 1.26 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{27}H_{29}O_{12}$ 545.1659, found 545.1666.

GC-1-benzoate (32). To a solution of **28** (5.3 mg, 8.0 mmol) in acetonitrile (100 mL) and $CHCl_3$ (32 mL) was added aq. solution of $(NH_4)_2Ce(NO_3)_6$ (9.8 mL, 16 mmol, 2 equiv, 1.63M). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (4.9 mL, 8 mmol, 1 equiv, 1.63M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40 – 70% EtOAc/hexanes) to obtain **32** as a white powder (2.6 mg, 60%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H_{AR}), 7.67 – 7.58 (m, 1H_{AR}), 7.51 – 7.41 (m, 2H_{AR}), 6.05 (s, 1H, 12-H), 5.77 (d, J = 6.8 Hz, 1H, 1-H), 5.47 (d, J = 4.3 Hz, 1H, 6-H), 5.09 (d, J = 1.9 Hz, 1H, 10-H), 4.77 (d, J = 6.8 Hz, 1H, 2-H), 4.40 – 4.28 (m, 1H, 7-H), 3.56 (d, J = 1.9 Hz, 1H, 10-OH), 3.22 (q,

J = 7.1 Hz, 1H, 14-H), 2.86 (s, 1H, 3-OH), 2.25 (d, J = 11.7 Hz, 1H, 7-OH), 1.75 (d, J = 12.3 Hz, 1H, 8-H), 1.33 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.19 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for C$_{27}$H$_{29}$O$_{12}$
5 545.1659, found 545.1641.

7-(4-Nitro-phenoxycarbonyloxy)-10-Benzyloxy-GC (33). To a solution of **16** (34.7 mg, 0.065 mmol) in CH$_2$Cl$_2$ (0.82 mL) and pyridine (187 mL, 2.31 mmol, 35 equiv) was added solution of
10 p-nitrophenyl chloroformate (39.6 mg, 0.195 mmol, 3 equiv) in CH$_2$Cl$_2$ (0.3 mL). The mixture was stirred for 50 min and then quenched with aq. HCl (2 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was recrystalized from CHCl$_3$ to obtain **33** as a white crystals (27.8 mg, 61%). ^{1}H-NMR
15 (300 MHz, CDCl$_3$) δ 8.36 - 8.27 (m, 2H$_{AR}$), 7.50 - 7.32 (m, 7H$_{AR}$), 6.07 (s, 1H, 12-H), 5.47 (d, J = 9.4 Hz, 1H, benzyl), 5.47 (d, J = 4.3 Hz, 1H, 6-H), 5.08 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 4.99 (s, 1H, 10-H), 4.72 (d, J = 9.4 Hz, 1H, benzyl), 4.51 (d, J = 7.8 Hz, 1H, 2-H), 4.25 (dd, J = 7.8, 3.5 Hz, 1H, 1-H),
20 3.05 (q, J = 7.0 Hz, 1H, 14-H), 2.88 (bs, 1H, 3-OH), 2.79 (d, J = 3.5 Hz, 1H, 1-OH), 2.18 (d, J = 12.8 Hz, 1H, 8-H), 1.32 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.23 (s, 9H, tBu).

7-Methylcarbamoyloxy-10-benzyloxy-GC (34). To a solution of
25 **33** (6.4 mg, 9.3 mmol) in THF (0.17 mL) was added MeNH$_2$ in THF (14 mL, 28 mmol, 3 equiv, 2M). The mixture was stirred for 25 min and then quenched with sat. aq. NH$_4$Cl, extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (40 - 50% EtOAc/hexanes) to obtain **34** as
30 a white solid (4.8 mg, 88%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.50 - 7.37 (m, 5H$_{AR}$), 6.02 (s, 1H, 12-H), 5.44 (d, J = 9.4 Hz, 1H, benzyl), 5.28 (d, J = 4.4 Hz, 1H, 6-H), 5.21 (dd, J = 12.8, 4.4 Hz, 1H, 7-H), 4.96 (s, 1H, 10-H), 4.84 (bq, J ~ 4.8 Hz, 1H, -NH-), 4.73 (d, J = 9.4 Hz, 1H, benzyl), 4.49 (d, J = 7.8

Hz, 1H, 2-H), 4.21 (dd, J = 7.8, 3.4 Hz, 1H, 1-H), 3.03 (q, J = 7.0 Hz, 1H, 14-H), 2.92 (s, 1H, 3-OH), 2.86 (d, J = 4.9 Hz, 3H, CH_3), 2.80 (d, J = 3.4 Hz, 1H, 1-OH), 2.00 (d, J = 12.8 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.16 (s, 9H, tBu);

5   ^{13}C-NMR (75 MHz, $CDCl_3$) δ 7.25, 27.72, 29.31, 32.12, 41.58, 48.50, 63.90, 67.65, 74.02, 74.10, 74.20, 75.36, 77.30, 83.41, 90.61, 98.37, 109.92, 128.82, 129.53, 129.78, 134.15, 154.68, 170.59, 171.04, 175.17; HRMS (FAB) calcd for $C_{29}H_{34}O_{12}N$ 588.2081, found 588.2069.

10

7-tert-Butylcarbamoyloxy-10-benzyloxy-GC (35). To a solution of **33** (5.5 mg, 7.9 mmol) in THF (0.16 mL) was added t-BuNH$_2$ (3.4 mL, 32 mmol, 4 equiv). The mixture was stirred for 40 min and then quenched with aq. HCl (1 mL, 1M), extracted with

15   EtOAc (3x) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30 – 50% EtOAc/hexanes) to obtain **35** as a white solid (4.4 mg, 88%). The product was further purified by reverse phase HPLC. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 5H$_{AR}$), 6.02 (s, 1H, 12-H), 5.43 (d, J

20   = 9.5 Hz, 1H, benzyl), 5.28 (d, J = 4.2 Hz, 1H, 6-H), 5.18 (dd, J = 12.5, 4.2 Hz, 1H, 7-H), 4.96 (s, 1H, 10-H), 4.79 (s, 1H, -NH-), 4.75 (d, J = 9.5 Hz, 1H, benzyl), 4.50 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (dd, J = 7.9, 3.4 Hz, 1H, 1-H), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.81 (d, J = 3.4 Hz, 1H, 1-OH), 2.69 (s,

25   1H, 3-OH), 1.98 (d, J = 12.8 Hz, 1H, 8-H), 1.35 (s, 9H, tBu), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.15 (s, 9H, tBu); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 7.21, 28.82, 29.33, 32.10, 41.53, 48.65, 50.93, 63.95, 67.65, 73.38, 74.07, 74.10, 75.39, 77.56, 83.43, 90.56, 98.34, 109.97, 128.85, 129.50, 129.73, 134.16, 152.11,

30   170.62, 171.09, 175.08; HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{32}H_{39}O_{12}NNa$ 652.2370, found 652.2368.

7-(Morpholine-4-carbonyloxy)-10-benzyloxy-GC (36). To a solution of **33** (5.2 mg, 7.5 mmol) in THF (0.15 mL) was added morpholine (2 mL, 23 mmol, 3 equiv). The mixture was stirred for 25 min and then quenched with aq. HCl (1 mL, 1M),

5   extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (40 – 50% EtOAc/hexanes) to obtain **36** as a white solid (6.0 mg, 92%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.49 – 7.38 (m, 5H$_{AR}$), 6.03 (s, 1H, 12-H), 5.44 (d, J = 9.4 Hz, 1H, benzyl), 5.32 – 5.23 (m, 2H,

10 6-H & 7-H), 4.97 (s, 1H, 10-H), 4.74 (d, J = 9.4 Hz, 1H, benzyl), 4.48 (d, J = 7.8 Hz, 1H, 2-H), 4.22 (dd, J = 7.8, 3.5 Hz, 1H, 1-H), 3.77 – 3.33 (m, 8H, morph.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.93 (s, 1H, 3-OH), 2.80 (d, J = 3.5 Hz, 1H, 1-OH), 2.09 – 2.00 (m, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-

15 CH$_3$), 1.17 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.27, 29.31, 32.13, 41.57, 44.21 (morph.), 44.48 (morph.), 48.62, 63.94, 66.48 (morph.), 66.59 (morph.), 67.56, 73.97, 74.06, 74.68, 75.30, 77.14, 83.40, 90.58, 98.39, 109.88, 128.80, 129.51, 129.78, 134.10, 152.99, 170.53, 171.02, 175.16; HRMS (FAB)

20 calcd for C$_{32}$H$_{38}$O$_{13}$N 644.2343, found 644.2333.

7-(Piperidine-carbonyloxy)-10-benzyloxy-GC (37). To a solution of **33** (5.0 mg, 7.2 mmol) in THF (0.15 mL) was added piperidine (2.1 mL, 22 mmol, 3 equiv). The mixture was stirred for 30

25 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 – 40% EtOAc/hexanes) to obtain **37** as a white solid (3.8 mg, 81%). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.50 – 7.37 (m, 5H$_{AR}$), 6.03 (s, 1H, 12-H), 5.43 (d, J

30 = 9.4 Hz, 1H, benzyl), 5.32 – 5.23 (m, 2H, 6-H & 7-H), 4.97 (s, 1H, 10-H), 4.74 (d, J = 9.4 Hz, 1H, benzyl), 4.48 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (dd, J = 7.8, 3.4 Hz, 1H, 1-H), 3.57 – 3.33 (m, 4H, piper.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.79 (d, J = 3.4 Hz, 1H, 1-OH), 2.78 (s, 1H, 3-OH), 2.10 – 1.99 (m, 1H,

8-H), 1.71 - 1.40 (m, 6H, piper.), 1.30 (d, J = 7.0 Hz, 3H, 16-CH_3), 1.17 (s, 9H, tBu); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 7.25, 24.22 (piper.), 25.55 (piper.), 25.89 (piper.), 29.31, 32.12, 41.56, 45.20 (piper.), 48.66, 63.97, 67.57, 74.01, 74.04 ,

5   74.37, 75.33, 77.23, 83.39, 90.58, 98.37, 109.93, 128.80, 129.50, 129.73, 134.13, 152.94, 170.63, 171.12, 175.14; HRMS (FAB) calcd for $C_{33}H_{40}O_{12}N$ 642.2551, found 642.2579.

1-Methylcarbamoyloxy-10-benzyloxy-GC (39). To a solution of

10   **16** (9.3 mg, 17.6 mmol) in CH_2Cl_2 (110 mL) and iPr$_2$EtN (18.4 mL, 0.105 mmol, 6 equiv), was added a solution of p-nitrophenyl chloroformate (10.6 mg, 52.6 mmol, 3 equiv) in CH_2Cl_2 (50 mL). The mixture was stirred for 16 min and MeNH$_2$ (2M in THF, 26 mL, 52.6 mmol, 3 equiv) and THF (80 mL) were added. The mixture

15   was then stirred for additional 25 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (50 - 100% EtOAc/hexanes) to obtain **39** as a white solid (6.6 mg, 64%). ^{1}H-NMR (300 MHz, 320K, $CDCl_3$) δ 7.42 - 7.2 (m, 5H$_{AR}$),

20   5.96 (s, 1H, 12-H), 5.55 (d, J = 6.0 Hz, 1H, 1-H), 5.39 (d, J = 11.5 Hz, 1H, benzyl), 5.19 (d, J = 4.3 Hz, 1H, 6-H), 4.82 (s, 1H, 10-H), 4.64 (bd, J = 11.5 Hz, 1H, benzyl), 4.62 (d, J = 6.0 Hz, 1H, 2-H), 4.38 - 4.25 (m, 1H, 7-H), 4.26 (m, 1H, -NH-), 3.20 (q, J = 7.2 Hz, 1H, 14-H), 2.92 (s, 1H, 3-OH), 2.29

25   (bd, J ~ 4.1 Hz, 3H, CH_3), 2.16 (d, J = 11.5 Hz, 1H, 7-OH), 1.69 (d, J = 12.3 Hz, 1H, 8-H), 1.31 (d, J = 7.2 Hz, 3H, 16-CH_3), 1.15 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{29}H_{34}O_{12}N$ 588.2081, found 588.2103.

30

1-tert-Butylcarbamoyloxy-10-benzyloxy-GC (40). To a solution of **16** (3.7 mg, 7.0 mmol) in CH_2Cl_2 (50 mL) and iPr$_2$EtN (7.3 mL, 42 mmol, 6 equiv), was added solution of p-nitrophenyl chloroformate (4.2 mg, 21 mmol, 3 equiv) in CH_2Cl_2 (20 mL).

The mixture was stirred for 16 min and tBuNH$_2$ (7.4 mL, 70 mmol, 10 equiv) and THF (40 mL) were added. The mixture was then stirred for additional 12 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The

5   crude product was purified by flash chromatography (40 - 50% EtOAc/hexanes) to obtain **40** as a white solid (2.6 mg, 59%). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.40 - 7.22 (m, 5H$_{AR}$), 5.93 (s, 1H, 12-H), 5.55 (d, J = 5.1 Hz, 1H, 1-H), 5.32 (d, J = 12.3 Hz, 1H, benzyl), 5.22 (d, J = 4.3 Hz, 1H, 6-H), 4.81 (bd, J = 11.5

10   Hz, 1H, benzyl), 4.79 (s, 1H, 10-H), 4.67 (d, J = 5.1 Hz, 1H, 2-H), 4.53 (bs, 1H, -NH-), 4.36 - 4.24 (m, 1H, 7-H), 3.21 (q, J = 7.3 Hz, 1H, 14-H), 3.17 (bs, 1H, 3-OH), 2.13 (bd, J = 12.0 Hz, 1H, 7-OH), 1.65 (d, J = 12.3 Hz, 1H, 8-H), 1.32 (d, J = 7.3 Hz, 3H, 16-CH$_3$), 1.12 (s, 9H, tBu), 1.03 (s, 9H, tBu); ^{13}C-

15   NMR (100 MHz, CDCl$_3$) δ 8.57, 28.49, 28.97, 32.16, 40.94, 50.43, 50.75, 65.05, 66.53, 74.61, 74.94, 75.19, 80.10, 84.08, 91.90, 99.96, 108.52, 127.85, 128.12 (2), 135.55, 151.09, 169.47, 170.34, 174.20; HRMS (FAB) calcd for C$_{32}$H$_{40}$O$_{12}$N 630.2551, found 630.2554.

20

1-(Morpholine-4-carbonyloxy)-10-benzyloxy-GC   **(41).**   To   a solution of **16** (6.3 mg, 12.0 mmol) in CH$_2$Cl$_2$ (350 mL) and iPr$_2$EtN (12.5 mL, 72 mmol, 6 equiv), was added solution of p-nitrophenyl chloroformate (7.2 mg, 36 mmol, 3 equiv) in CH$_2$Cl$_2$

25   (50 mL). The mixture was stirred for 30 min and morpholine (6.3 mL, 72 mmol, 6 equiv) was added. The mixture was then stirred for additional 2 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (50 - 100%

30   EtOAc/hexanes) to obtain **41** as a white solid (6.0 mg, 78%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.41 - 7.31 (m, 3H$_{AR}$), 7.29 - 7.21 (m, 2H$_{AR}$), 5.99 (s, 1H, 12-H), 5.60 (d, J = 5.6 Hz, 1H, 1-H), 5.40 (d, J = 11.5 Hz, 1H, benzyl), 5.15 (d, J = 4.4 Hz, 1H, 6-H), 4.85 (s, 1H, 10-H), 4.71 (d, J = 5.6 Hz, 1H, 2-H), 4.62

(d, J = 11.5 Hz, 1H, benzyl), 4.38 - 4.28 (m, 1H, 7-H), 3.60
(s, 1H, 3-OH), 3.5 - 3.2 (m, 6H, morph.), 3.21 (q, J = 7.2 Hz,
1H, 14-H), 2.78 - 2.67 (m, 1H, morph.), 2.50 (d, J = 11.7 Hz,
1H, 7-OH), 2.49 - 2.38 (m, 1H, morph.), 1.72 (d, J = 12.3 Hz,
5   1H, 8-H), 1.32 (d, J = 7.2 Hz, 3H, 16-CH$_3$), 1.18 (s, 9H, tBu);
^{13}C-NMR (75 MHz, CDCl$_3$) δ 8.30, 29.16, 32.40, 41.19, 43.48,
43.73, 50.40, 65.07, 65.87, 66.15, 66.51, 73.24, 75.65, 75.85,
80.21, 84.12, 92.16, 99.90, 109.11, 127.44, 128.42, 128.65,
136.20, 152.15, 169.99, 170.60, 175.04; HRMS (FAB) calcd for
10   C$_{32}$H$_{38}$O$_{13}$N 644.2343, found 644.2355.

1-(Piperidine-carbonyloxy)-10-benzyloxy-GC   **(42).**   To   a
solution of **16** (11.3 mg, 21.3 mmol) in CH$_2$Cl$_2$ (710 mL) and
iPr$_2$EtN (22.4 mL, 128 mmol, 6 equiv), was added solution of p-
15   nitrophenyl chloroformate (13 mg, 64 mmol, 3 equiv) in CH$_2$Cl$_2$
(80 mL). The mixture was stirred for 30 min and piperidine
(12.6 mL, 128 mmol, 6 equiv) was added. The mixture was then
stirred for additional 2 h and then quenched with aq. HCl (1
mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The
20   crude product was purified by flash chromatography (35 - 70%
EtOAc/hexanes) to obtain **42** as a white solid (6.8 mg, 50%).
^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.39 - 7.28 (m, 3H$_{AR}$) , 7.28 - 7.21
(m, 2H$_{AR}$), 5.97 (s, 1H, 12-H), 5.57 (d, J = 5.3 Hz, 1H, 1-H),
5.38 (d, J = 11.5 Hz, 1H, benzyl), 5.14 (d, J = 4.4 Hz, 1H, 6-
25   H), 4.84 (s, 1H, 10-H), 4.72 (d, J = 5.3 Hz, 1H, 2-H), 4.65
(d, J = 11.5 Hz, 1H, benzyl), 4.37 - 4.28 (m, 1H, 7-H), 3.57
(s, 1H, 3-OH), 3.50 - 3.38 (m, 1H, piper.), 3.35 - 3.23 (m,
1H, piper.), 3.22 (q, J = 7.3 Hz, 1H, 14-H), 2.60 - 2.49 (m,
1H, piper.), 2.47 - 2.37 (m, 1H, piper.), 2.36 (d, J = 12.0
30   Hz, 1H, 7-OH), 1.70 (d, J = 12.3 Hz, 1H, 8-H), 1.61 - 1.50 (m,
1H, piper.), 1.45 - 1.25 (m, 5H, piper.), 1.32 (d, J = 7.3 Hz,
3H, 16-CH$_3$), 1.16 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 8.53,
23.89, 24.96, 25.52, 29.17, 32.38, 41.15, 44.49, 44.64, 50.47,
65.17, 66.80, 73.12, 75.44, 75.64, 76.07, 80.39, 84.26, 92.23,

100.23, 108.98, 127.75, 128.17, 128.54, 136.16, 152.22, 170.02, 170.80, 175.00; HRMS (FAB) calcd for $C_{33}H_{40}O_{12}N$ 642.2551, found 642.2521.

5   **7-(4-Nitro-phenoxycarbonyloxy)-10-(4-methoxy-benzyloxy)-GC (43).** To a solution of **24** (47.6 mg, 0.085 mmol) in CH_2Cl_2 (0.53 mL) and pyridine (121 mL, 1.50 mmol, 18 equiv) at 0°C was added solution of p-nitrophenyl chloroformate (34.2 mg, 0.170 mmol, 2 equiv) in CH_2Cl_2 (0.2 mL). The mixture was allowed to

10   warm up slowly to room temperature while stirring. After 2.5 h the reaction was quenched with aq. HCl (2 mL, 1M), extracted with EtOAc (3x) and dried with $MgSO_4$. The crude product was purified by flash chromatography (30 - 50% EtOAc/hexanes) to obtain **43** as a white powder (42.6 mg, 69%) and unreacted

15   starting material **24** (9.5 mg, 20%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.35 - 8.27 (m, 2H$_{AR}$), 7.46 - 7.38 (m, 2H$_{AR}$), 7.35 - 7.28 (m, 2H$_{AR}$), 6.95 - 6.88 (m, 2H$_{AR}$), 6.06 (s, 1H, 12-H), 5.45 (d, J = 4.3 Hz, 1H, 6-H), 5.38 (d, J = 9.3 Hz, 1H, benzyl), 5.05 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 4.98 (s, 1H, 10-H), 4.66 (d, J =

20   9.3 Hz, 1H, benzyl), 4.51 (d, J = 7.8 Hz, 1H, 2-H), 4.25 (dd, J = 7.8, 3.5 Hz, 1H, 1-H), 3.80 (s, 3H, -OMe), 3.06 (q, J = 7.0 Hz, 1H, 14-H), 3.04 (s, 1H, 3-OH), 2.87 (d, J = 3.5 Hz, 1H, 1-OH), 2.17 (d, J = 12.8 Hz, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.22 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ

25   7.46, 29.42, 32.24, 41.70, 48.48, 55.38, 63.85, 67.77, 73.72, 73.90, 74.93, 75.69, 78.17, 83.43, 90.48, 98.23, 109.65, 114.71, 121.48, 125.28, 125.94, 130.36, 145.52, 150.82, 154.72, 160.41, 170.07, 170.11, 174.90.

30   **7-Methylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (44).** To a solution of **43** (14.2 mg, 19.5 mmol) in THF (0.20 mL) was added MeNH$_2$ in THF (29 mL, 59 mmol, 3 equiv, 2M). The mixture was stirred for 20 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with $MgSO_4$. The crude

product was purified by flash chromatography (40 – 70% EtOAc/hexanes) to obtain **44** as a white solid (8.9 mg, 74%). ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.36 (d, J = 8.5 Hz, 2H$_{AR}$), 6.95 (d, J = 8.5 Hz, 2H$_{AR}$), 6.01 (s, 1H, 12-H), 5.35 (d, J = 9.3 Hz, 1H,

5 benzyl), 5.26 (d, J = 4.3 Hz, 1H, 6-H), 5.19 (dd, J = 12.8, 4.4 Hz, 1H, 7-H), 4.94 (s, 1H, 10-H), 4.83 (bq, J ~ 4.8 Hz, 1H, -NH-), 4.67 (d, J = 9.3 Hz, 1H, benzyl), 4.49 (d, J = 7.8 Hz, 1H, 2-H), 4.20 (dd, J = 7.8, 3.3 Hz, 1H, 1-H), 3.82 (s, 3H, -OMe), 3.03 (q, J = 7.0 Hz, 1H, 14-H), 2.90 (s, 1H, 3-OH),

10 2.89 – 2.80 (m, 4H, CH$_3$ & 1-OH), 1.99 (d, J = 12.8 Hz, 1H, 8-H), 1.29 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.15 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.24, 27.61, 29.21, 32.01, 41.47, 48.35, 55.14, 63.70, 67.43, 73.40, 73.77, 73.96, 74.78, 83.15, 90.31, 98.01, 109.55, 114.45, 125.81, 130.13, 154.19, 160.10, 170.15,

15 170.52, 174.69; HRMS (FAB) calcd for C$_{30}$H$_{34}$O$_{13}$N 616.2030, found 616.2056.

7-*tert*-Butylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (45). To a solution of **43** (14.2 mg, 19.5 mmol) in THF (0.20 mL) was

20 added t-BuNH$_2$ (6.2 mL, 59 mmol, 3 equiv). The mixture was stirred for 40 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 – 70% EtOAc/hexanes) to obtain **45** as a white solid (10.0 mg, 77%).

25 ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.35 (m, 2H$_{AR}$), 6.99 – 6.91 (m, 2H$_{AR}$), 6.01 (s, 1H, 12-H), 5.34 (d, J = 9.3 Hz, 1H, benzyl), 5.26 (d, J = 4.3 Hz, 1H, 6-H), 5.15 (dd, J = 12.8, 4.2 Hz, 1H, 7-H), 4.94 (s, 1H, 10-H), 4.81 (s, 1H, -NH-), 4.69 (d, J = 9.3 Hz, 1H, benzyl), 4.50 (d, J = 7.9 Hz, 1H, 2-H), 4.20 (dd, J =

30 7.9, 3.4 Hz, 1H, 1-H), 3.82 (s, 3H, -OMe), 3.03 (q, J = 7.0 Hz, 1H, 14-H), 2.94 (s, 1H, 3-OH), 2.88 (d, J = 3.4 Hz, 1H, 1-OH), 1.97 (d, J = 12.8 Hz, 1H, 8-H), 1.35 (s, 9H, tBu), 1.29 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.15 (s, 9H, tBu); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 7.27, 28.79, 29.31, 32.08, 41.60, 48.60, 50.89,

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55.30, 63.90, 67.61, 73.35, 73.62, 74.01, 75.02, 77.55, 83.42, 90.58, 98.34, 109.96, 114.76, 126.24, 130.63, 152.11, 160.56, 170.78, 171.18, 175.29; HRMS (FAB) calcd for $C_{33}H_{41}O_{13}N$ 659.2578, found 659.2582.

7-(Morpholine-4-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (46). To a solution of **43** (11.4 mg, 15.7 mmol) in THF (0.20 mL) was added morpholine (6.8 mL, 78 mmol, 5 equiv). The mixture was stirred for 25 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 – 70% EtOAc/hexanes) to obtain **46** as a white solid (9.5 mg, 90%). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.36 (d, J = 8.6 Hz, 2H$_{AR}$), 6.95 (d, J = 8.6 Hz, 2H$_{AR}$), 6.02 (s, 1H, 12-H), 5.36 (d, J = 9.3 Hz, 1H, benzyl), 5.30 – 5.19 (m, 2H, 6-H & 7-H), 4.95 (s, 1H, 10-H), 4.68 (d, J = 9.3 Hz, 1H, benzyl), 4.48 (d, J = 7.8 Hz, 1H, 2-H), 4.21 (d, J = 7.8 Hz, 1H, 1-H), 3.82 (s, 3H, -OMe), 3.78 – 3.33 (m, 8H, morph.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.85 (bs, 2H, 3-OH & 1-OH), 2.09 – 1.99 (m, 1H, 8-H), 1.30 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.16 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.24, 29.23, 32.04, 41.45, 44.08 (morph.), 44.35 (morph.), 48.54, 55.14, 63.78, 66.29 (morph.), 66.36 (morph.), 67.38, 73.40, 73.76, 74.47, 74.76, 76.92, 83.15, 90.29, 98.04, 109.53, 114.45, 125.79, 130.13, 152.52, 160.11, 170.08, 170.48, 174.59; HRMS (FAB) calcd for $C_{33}H_{39}O_{14}N$ 673.2371, found 673.2402.

7-(Piperidine-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (47). To a solution of **43** (14.2 mg, 19.5 mmol) in THF (0.20 mL) was added piperidine (5.8 mL, 59 mmol, 3 equiv). The mixture was stirred for 30 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (30 – 50% EtOAc/hexanes) to obtain **47** as a white solid (11.3 mg, 86%).

^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.36 (d, J = 8.7 Hz, 2H$_{AR}$), 6.94 (d, J = 8.7 Hz, 2H$_{AR}$), 6.01 (s, 1H, 12-H), 5.35 (d, J = 9.3 Hz, 1H, benzyl), 5.29 - 5.20 (m, 2H, 6-H & 7-H), 4.95 (s, 1H, 10-H), 4.68 (d, J = 9.3 Hz, 1H, benzyl), 4.48 (d, J = 7.9 Hz, 1H, 2-

5   H), 4.20 (dd, J = 7.9, 3.4 Hz, 1H, 1-H), 3.81 (s, 3H, -OMe), 3.53 - 3.37 (m, 4H, piper.), 3.04 (q, J = 7.0 Hz, 1H, 14-H), 2.95 (s, 1H, 3-OH), 2.86 (d, J = 3.4 Hz, 1H, 1-OH), 2.03 (d, J = 12.2 Hz, 1H, 8-H), 1.68 - 1.42 (m, 6H, piper.), 1.30 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.16 (s, 9H, tBu); ^{13}C-NMR (100 MHz, CDCl$_3$)

10   δ 7.51, 24.39 (piper.), 25.71 (piper.), 26.07 (piper.), 29.47, 32.27, 41.74, 45.25 (piper.), 48.80, 55.38, 64.03, 67.62, 73.60, 74.04, 74.44, 75.01, 77.41, 83.39, 90.59, 98.32, 109.85, 114.68, 126.09, 130.39, 152.74, 160.31, 170.47, 170.85, 174.96; HRMS (FAB) calcd for C$_{34}$H$_{40}$O$_{13}$N 670.2500, found

15   670.2526.

1-Methylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (49). To a solution of **24** (11.1 mg, 19 mmol) in CH$_2$Cl$_2$ (120 mL) and

20   iPr$_2$EtN (20.8 mL, 0.114 mmol, 6 equiv), was added solution of p-nitrophenyl chloroformate (12.0 mg, 57 mmol, 3 equiv) in CH$_2$Cl$_2$ (56 mL). The mixture was stirred for 15 min and MeNH$_2$ (2M in THF, 30 mL, 57 mmol, 3 equiv) and THF (50 mL) were added. The mixture was then stirred for additional 25 min and

25   then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (50 - 100% EtOAc/hexanes) to obtain **49** as a white solid (8.2 mg, 67%). ^{1}H-NMR (400 MHz, CDCl$_3$, T = 330K) δ 7.25 - 7.15 (m, 2H$_{AR}$), 6.90 - 6.80 (m, 2H$_{AR}$), 5.94 (s, 1H, 12-

30   H), 5.53 (d, J = 5.7 Hz, 1H, 1-H), 5.24 (d, J = 11.1 Hz, 1H, benzyl), 5.18 (d, J = 4.3 Hz, 1H, 6-H), 4.79 (s, 1H, 10-H), 4.69 - 4.54 (m, 2H, 2-H & benzyl), 4.39 (bs, 1H, -NH-), 4.32 - 4.21 (m, 1H, 7-H), 3.80 (s, 3H, -OMe), 3.19 (q, J = 7.2 Hz, 1H, 14-H), 3.01 (s, 1H, 3-OH), 2.42 (bs, 3H, -CH$_3$), 2.19 (d, J

J = 10.8 Hz, 1H, 7-OH), 1.68 (d, J = 12.3 Hz, 1H, 8-H), 1.30 (d, J = 7.2 Hz, 3H, 16-CH$_3$), 1.13 (s, 9H, tBu); ^{13}C-NMR (75 MHz, CD$_3$OD, T=320K) δ 9.42, 27.31, 29.63, 33.17, 42.59, 51.35, 55.86, 66.20, 68.12, 73.68, 76.12, 77.03, 77.21, 81.36, 85.44,

5   94.34, 102.23, 110.68, 114.84, 114.94, 130.42, 156.56, 161.06, 172.52, 172.80, 177.90; HRMS (FAB) calcd for C$_{30}$H$_{34}$O$_{13}$N 616.2030, found 616.2028.

1-tert-Butylcarbamoyloxy-10-(4-methoxy-benzyloxy)-GC (50). To

10   a solution of **24** (9.3 mg, 16.6 mmol) in CH$_2$Cl$_2$ (110 mL) and iPr$_2$EtN (17.4 mL, 99 mmol, 6 equiv), was added solution of p-nitrophenyl chloroformate (10.0 mg, 50 mmol, 3 equiv) in CH$_2$Cl$_2$ (40 mL). The mixture was stirred for 15 min and tBuNH$_2$ (17.4 mL, 166 mmol, 10 equiv) and THF (100 mL) were added. The

15   mixture was then stirred for additional 12 h and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$. The crude product was purified by flash chromatography (40 – 100% EtOAc/hexanes) to obtain **50** as a white solid (6.6 mg, 60%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.23 (d,

20   J = 8.6 Hz, 2H$_{AR}$), 6.86 (d, J = 8.6 Hz, 2H$_{AR}$), 5.91 (s, 1H, 12-H), 5.55 (d, J = 4.6 Hz, 1H, 1-H), 5.21 (d, J = 4.3 Hz, 1H, 6-H), 5.15 (d, J = 11.8 Hz, 1H, benzyl), 4.82 (bd, J = 11.8 Hz, 1H, benzyl), 4.75 (s, 1H, 10-H), 4.67 (d, J = 5.0 Hz, 1H, 2-H), 4.62 (bs, 1H, -NH-), 4.30 – 4.19 (m, 1H, 7-H), 3.80 (s,

25   3H, -OMe), 3.23 (bs, 1H, 3-OH), 3.20 (q, J = 7.3 Hz, 1H, 14-H), 2.17 (d, J = 11.8 Hz, 1H, 7-OH), 1.63 (d, J = 12.3 Hz, 1H, 8-H), 1.32 (d, J = 7.3 Hz, 3H, 16-CH$_3$), 1.19 (s, 9H, tBu), 1.01 (s, 9H, tBu); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 8.68, 28.72, 29.02, 32.20, 41.06, 50.51, 50.92, 55.31, 65.29, 66.83, 72.16, 73.96,

30   75.27, 80.41, 84.41, 92.26, 100.34, 108.79, 113.88, 127.77, 130.14, 151.70, 159.72, 170.25, 171.01, 174.94; HRMS (FAB) calcd for C$_{33}$H$_{40}$O$_{13}$N 658.2500, found 658.2516.

1-(Morpholine-4-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (51).
To a solution of **24** (10.8 mg, 19.3 mmol) in CH_2Cl_2 (118 mL) and
iPr_2EtN (20.3 mL, 116 mmol, 6 equiv), was added solution of p-
nitrophenyl chloroformate (11.7 mg, 58 mmol, 3 equiv) in CH_2Cl_2

5 (55 mL). The mixture was stirred for 15 min and morpholine
(13.5 mL, 154 mmol, 8 equiv) and THF (100mL) were added. The
mixture was then stirred for additional 35 min and then
quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x)
and dried with $MgSO_4$. The crude product was purified by flash

10 chromatography (50 - 100% EtOAc/hexanes) to obtain **51** as a
white solid (9.8 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (d,
J = 8.5 Hz, $2H_{AR}$), 6.88 (d, J = 8.5 Hz, $2H_{AR}$), 5.97 (s, 1H, 12-
H), 5.57 (d, J = 5.3 Hz, 1H, 1-H), 5.23 (d, J = 11.0 Hz, 1H,
benzyl), 5.11 (d, J = 4.3 Hz, 1H, 6-H), 4.82 (s, 1H, 10-H),

15 4.71 (d, J = 5.3 Hz, 1H, 2-H), 4.62 (d, J = 11.0 Hz, 1H,
benzyl), 4.32 - 4.21 (m, 1H, 7-H), 3.82 (s, 3H, -OMe), 3.57
(s, 1H, 3-OH), 3.54 - 3.33 (m, 5H, morph.), 3.31 - 3.18 (m,
1H, morph.), 3.21 (q, J = 7.2 Hz, 1H, 14-H), 2.89 - 2.66 (m,
2H, morph.), 2.39 (d, J = 11.7 Hz, 1H, 7-OH), 1.69 (d, J =

20 12.3 Hz, 1H, 8-H), 1.32 (d, J = 7.2 Hz, 3H, 16-CH_3), 1.15 (s,
9H, tBu); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.49, 29.14, 32.33, 41.16,
43.84 (morph.), 50.41, 55.41, 65.12, 65.94 (morph.), 66.21
(morph.), 66.68, 72.83, 74.97, 75.54, 76.28, 80.20, 84.25,
92.15, 100.08, 108.99, 113.97, 128.01, 129.64, 152.38, 159.75,

25 170.21, 170.66, 175.06; HRMS (FAB) calcd for $C_{33}H_{38}O_{14}N$
672.2292, found 672.2307.

1-(Piperidine-carbonyloxy)-10-(4-methoxy-benzyloxy)-GC (52).
To a solution of **24** (10.9 mg, 19.4 mmol) in CH_2Cl_2 (119 mL) and

30 iPr_2EtN (20.3 mL, 116 mmol, 6 equiv), was added solution of p-
nitrophenyl chloroformate (11.7 mg, 58 mmol, 3 equiv) in CH_2Cl_2
(55 mL). The mixture was stirred for 15 min and piperidine
(15.4 mL, 155 mmol, 8 equiv) and THF (100 ml) were added. The
mixture was then stirred for additional 30 min and then

quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with $MgSO_4$. The crude product was purified by flash chromatography (40 – 70% EtOAc/hexanes) to obtain **52** as a white solid (6.9 mg, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (d,
5   J = 8.6 Hz, $2H_{AR}$), 6.87 (d, J = 8.6 Hz, $2H_{AR}$), 5.95 (s, 1H, 12-H), 5.54 (d, J = 5.0 Hz, 1H, 1-H), 5.22 (d, J = 11.0 Hz, 1H, benzyl), 5.10 (d, J = 4.4 Hz, 1H, 6-H), 4.80 (s, 1H, 10-H), 4.72 (d, J = 5.0 Hz, 1H, 2-H), 4.64 (d, J = 11.0 Hz, 1H, benzyl), 4.32 – 4.22 (m, 1H, 7-H), 3.81 (s, 3H, -OMe), 3.55
10   (s, 1H, 3-OH), 3.52 – 3.40 (m, 1H, piper.), 3.32 – 3.19 (m, 1H, piper.), 3.22 (q, J = 7.3 Hz, 1H, 14-H), 2.77 – 2.56 (m, 2H, piper.), 2.25 (d, J = 12.0 Hz, 1H, 7-OH), 1.68 (d, J = 12.3 Hz, 1H, 8-H), 1.63 – 1.50 (m, 1H, piper.), 1.49 – 1.29 (m, 5H, piper.), 1.32 (d, J = 7.3 Hz, 3H, 16-CH_3), 1.14 (s, 9H,
15   tBu); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.68, 23.98 (piper.), 25.09 (piper.), 25.56 (piper.), 29.15, 32.31, 41.11, 44.62 (piper.), 44.84 (piper.), 50.53, 55.36, 65.25, 66.95, 72.68, 74.77, 75.56, 76.45, 80.38, 84.36, 92.18, 100.36, 108.86, 113.88, 128.07, 129.89, 152.37, 159.63, 170.20, 170.81, 174.88; HRMS
20   (FAB) calcd for $C_{34}H_{40}O_{13}N$ 670.2500, found 670.2510.

7-Methylcarbamoyloxy-GC (53). To a solution of **44** (5.3 mg, 8.7 mmol) in acetonitrile (108 mL) and $CHCl_3$ (35 mL) was added aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 mL, 17.3 mmol, 2 equiv,
25   1.63M). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 mL, 8.7 mmol, 1 equiv, 1.63M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40 – 99% EtOAc / 1% AcOH / hexanes) to obtain
30   **53** as a white powder (3.0 mg, 69%). ^{1}H-NMR (300 MHz, 315K, CD_3OD) δ 6.11 (s, 1H, 12-H), 5.32 (d, J = 4.3 Hz, 1H, 6-H), 5.18 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 5.13 (s, 1H, 10-H), 4.54 (d, J = 7.6 Hz, 1H, 2-H), 4.18 (d, J = 7.6 Hz, 1H, 1-H), 3.00 (q, J = 7.0 Hz, 1H, 14-H), 2.74 (s, 3H, CH_3), 2.00 (d, J = 12.9

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Hz, 1H, 8-H), 1.22 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.14 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for C$_{22}$H$_{28}$O$_{12}$N 498.1612, found 498.1633.

5   **7-$tert$-Butylcarbamoyloxy-GC (54)**. To a solution of **45** (5.7 mg, 8.6 mmol) in acetonitrile (108 mL) and CHCl$_3$ (35 mL) was added aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (10.6 mL, 17.3 mmol, 2 equiv, 1.63M). The mixture was stirred for 1.5 h, aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (5.3 mL, 8.7 mmol, 1 equiv, 1.63M) was added and
10   mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40 - 70% EtOAc / 1% AcOH / hexanes) to obtain **54** as a white powder (3.7 mg, 80%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 6.01 (bs, 1H, OH), 5.98 (s, 1H, 12-H), 5.42 (m, 1H, 6-H), 5.16
15   (dd, J = 12.8, 4.1 Hz, 1H, 7-H), 5.14 (s, 1H, 10-H), 4.96 (s, 1H, -NH-), 4.69 (d, J = 7.9 Hz, 1H, 2-H), 4.32 (bd, J = 7.9 Hz, 1H, 1-H), 4.23 (bs, 2H, OH), 3.14 (bq, J = 7.1 Hz, 1H, 14-H), 1.98 (d, J = 12.8 Hz, 1H, 8-H), 1.31 (s, 9H, tBu), 1.27 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.10 (s, 9H, tBu); HSQC
20   correlation data in the Supporting Information; HRMS (FAB) calcd for C$_{25}$H$_{34}$O$_{12}$N 540.2081, found 540.2098.

     7-(Morpholine-4-carbonyloxy)-GC (55). To a solution of **46** (5.8 mg, 8.7 mmol) in acetonitrile (108 mL) and CHCl$_3$ (35 mL)
25   was added aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (10.6 mL, 17.3 mmol, 2 equiv, 1.63M). The mixture was stirred for 1.5 h, aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (5.3 mL, 8.7 mmol, 1 equiv, 1.63M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified
30   by flash chromatography (50 - 99% EtOAc / 1% AcOH / hexanes) to obtain **55** as a white powder (2.9 mg, 60%). ^{1}H-NMR (400 MHz, CD$_3$OD) δ 6.14 (s, 1H, 12-H), 5.34 (d, J = 4.4 Hz, 1H, 6-H), 5.24 (dd, J = 12.8, 4.4 Hz, 1H, 7-H), 5.15 (s, 1H, 10-H), 4.54 (d, J = 7.6 Hz, 1H, 2-H), 4.18 (d, J = 7.6 Hz, 1H, 1-H), 3.73

– 3.37 (m, 8H, morph.), 3.00 (q, J = 7.1 Hz, 1H, 14-H), 2.06 (d, J = 12.8 Hz, 1H, 8-H), 1.22 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.15 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{25}H_{32}O_{13}N$ 554.1874, found 554.1874.

7-(Piperidine-carbonyloxy)-GC (56). To a solution of **47** (5.8 mg, 8.6 mmol) in acetonitrile (108 mL) and CHCl$_3$ (35 mL) was added aq. solution of $(NH_4)_2Ce(NO_3)_6$ (10.6 mL, 17.3 mmol, 2 equiv, 1.63M). The mixture was stirred for 1.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (5.3 mL, 8.7 mmol, 1 equiv, 1.63M) was added and mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and residue was purified by flash chromatography (40 – 70% EtOAc / 1% AcOH / hexanes) to obtain **56** as a white powder (3.0 mg, 64%). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 6.21 (bs, 1H, OH), 5.98 (s, 1H, 12-H), 5.41 (m, 1H, 6-H), 5.25 (dd, J = 12.8, 4.3 Hz, 1H, 7-H), 5.14 (s, 1H, 10-H), 4.68 (d, J = 7.9 Hz, 1H, 2-H), 4.36 (bs, 1H, OH), 4.32 (bd, J = 7.9 Hz, 1H, 1-H), 3.55 – 3.26 (m, 4H, piper.), 3.15 (m, 1H, 14-H), 2.04 (d, J = 12.8 Hz, 1H, 8-H), 1.75 – 1.40 (m, 6H, piper.), 1.26 (d, J = 7.0 Hz, 3H, 16-CH$_3$), 1.11 (s, 9H, tBu); HSQC HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{26}H_{34}O_{12}N$ 552.2081, found 552.2067.

1-Methylcarbamoyloxy-GC (57). To a solution of **49** (3.5 mg, 5.6 mmol) in acetonitrile (70 mL) and CHCl$_3$ (23 mL) was added aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M). The mixture was stirred for 6.5 h, aq. solution of $(NH_4)_2Ce(NO_3)_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M) was added and the mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography (70 – 99% EtOAc / 1% AcOH / hexanes) to obtain **57** as a white powder (2.4 mg, 86%). ^{1}H-NMR (400 MHz, CD$_3$OD) δ 6.06 (s, 1H, 12-H), 5.46 (d, J = 5.3 Hz, 1H, 1-H),

5.22 (d, J = 4.1 Hz, 1H, 6-H), 5.07 (s, 1H, 10-H), 4.66 (d, J = 5.5 Hz, 1H, 2-H), 4.31 (dd, J = 12.6, 4.1 Hz, 1H, 7-H), 3.10 (q, J = 7.2 Hz, 1H, 14-H), 2.83 – 2.68 (m, 3H, -CH$_3$), 1.78 (d, J = 12.5 Hz, 1H, 8-H), 1.27 (d, J = 7.2 Hz, 3H, 16-CH$_3$), 1.22

5   (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{22}H_{28}O_{12}N$ 498.1612, found 498.1618.

1-tert-Butylcarbamoyloxy-GC (58). To a solution of 50 (3.7

10   mg, 5.6 mmol) in acetonitrile (70 mL) and CHCl$_3$ (23 mL) was added aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M). The mixture was stirred for 6 h, aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M) was added and the mixture was further stirred for 12 h. Volatiles were

15   removed under reduced pressure and the residue was purified by flash chromatography (40 – 70% EtOAc/hexanes) to obtain 58 as a white powder (2.5 mg, 84%). ^{1}H-NMR (400 MHz, CD$_3$OD) δ 6.05 (s, 1H, 12-H), 5.45 (d, J = 5.1 Hz, 1H, 1-H), 5.28 (d, J = 4.2 Hz, 1H, 6-H), 5.06 (s, 1H, 10-H), 4.64 (d, J = 5.1 Hz, 1H, 2-

20   H), 4.33 (dd, J = 12.4, 4.2 Hz, 1H, 7-H), 3.10 (q, J = 7.3 Hz, 1H, 14-H), 1.77 (d, J = 12.4 Hz, 1H, 8-H), 1.34 (s, 9H, tBu), 1.27 (d, J = 7.3 Hz, 3H, 16-CH$_3$), 1.22 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for $C_{25}H_{34}O_{12}N$ 540.2081, found 540.2075.

25

1-(Morpholine-4-carbonyloxy)-GC (59). To a solution of 51 (6.5 mg, 9.6 mmol) in acetonitrile (120 mL) and CHCl$_3$ (39 mL) was added aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (11.8 mL, 19.2 mmol, 2 equiv, 1.63M). The mixture was stirred for 6.5 h, aq.

30   solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (11.8 mL, 19.2 mmol, 2 equiv, 1.63M) was added and the mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography (70 – 99% EtOAc / 1% AcOH / hexanes) to obtain 59 as a white powder (4.3 mg, 80%). ^{1}H-

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NMR (400 MHz, CD$_3$OD) δ 6.10 (s, 1H, 12-H), 5.39 (d, J = 6.6 Hz, 1H, 1-H), 5.22 (d, J = 4.2 Hz, 1H, 6-H), 5.09 (s, 1H, 10-H), 4.74 (d, J = 6.6 Hz, 1H, 2-H), 4.28 (dd, J = 12.4, 4.2 Hz, 1H, 7-H), 3.76 - 3.62 (m, 4H, morph.), 3.58 - 3.38 (m, 4H,

5   morph.), 3.12 (q, J = 7.1 Hz, 1H, 14-H), 1.79 (d, J = 12.4 Hz, 1H, 8-H), 1.28 (d, J = 7.1 Hz, 3H, 16-CH$_3$), 1.22 (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for C$_{25}$H$_{32}$O$_{13}$N 554.1874, found 554.1874.

10   **1-(Piperidine-carbonyloxy)-GC (60).** To a solution of 52 (3.8 mg, 5.6 mmol) in acetonitrile (70 mL) and CHCl$_3$ (23 mL) was added aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M). The mixture was stirred for 6.5 h, aq. solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (6.9 mL, 11.2 mmol, 2 equiv, 1.63M)

15   was added and the mixture was further stirred for 12 h. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography (50 - 100% EtOAc/hexanes) to obtain 60 as a white powder (2.5 mg, 79%). ^{1}H-NMR (400 MHz, CD$_3$OD) δ 6.09 (s, 1H, 12-H), 5.40 (d, J = 6.4 Hz, 1H, 1-H),

20   5.22 (d, J = 4.2 Hz, 1H, 6-H), 5.08 (s, 1H, 10-H), 4.71 (d, J = 6.4 Hz, 1H, 2-H), 4.32 (dd, J = 12.4, 4.2 Hz, 1H, 7-H), 3.68 - 3.50 (m, 2H, piper.), 3.46 - 3.20 (m, 2H, piper.), 3.12 (q, J = 7.2 Hz, 1H, 14-H), 1.79 (d, J = 12.4 Hz, 1H, 8-H), 1.75 - 1.52 (m, 6H, piper.), 1.28 (d, J = 7.2 Hz, 3H, 16-CH$_3$), 1.22

25   (s, 9H, tBu); HSQC correlation data in the Supporting Information; HRMS (FAB) calcd for C$_{26}$H$_{34}$O$_{12}$N 552.2081, found 552.2061.

10-benzyloxy-isoGC-1,6-carbonate (61): To a solution of 16

30   (9.6 mg, 18.2 mol) in CH$_2$Cl$_2$ (113 □L) and iPr$_2$EtN (19.1 L, 0.109 mmol, 6 equiv), was added solution of p-nitrophenyl chloroformate (11.0 mg, 54.6 □mol, 3 equiv) in CH$_2$Cl$_2$ (50 L). The mixture was stirred for 15 min and then quenched with aq. HCl (1 mL, 1M), extracted with EtOAc (3x) and dried with MgSO$_4$.

The crude product was purified by flash chromatography (30 - 50 % EtOAc/hexanes) to obtain **61** as a white solid (9.3 mg, 92 % yield, 82 % purity). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.45 - 7.28 (m, 5H$_{AR}$), 5.82 (s, 1H), 5.63 (s, 1H), 5.49 (d, J = 10.6 Hz,
5   1H), 5.05 (s, 1H), 4.88 (d, J = 4.0 Hz, 1H), 4.79 (d, J = 10.6 Hz, 1H), 4.76 (d, J = 4.0 Hz, 1H), 4.73 (s, 1H), 3.26 (q, J = 7.8 Hz, 1H), 2.96 (s, 1H), 2.28 (s, 1H), 1.35 (d, J = 7.8 Hz, 3H), 1.11 (s, 9H, tBu). MS (FAB) calcd for C$_{28}$H$_{29}$O$_{12}$ 557.17, found 557.56.

10

BIOLOGICAL TESTING

Functional glycine receptor assay. Pharmacological activities of the compounds were evaluated in a FLIPR® Membrane Potential Assay (Molecular Deives, Crawley, UK) using a HEK293 cell line
15   stably expressing the human homomeric α1 GlyR.[53] Briefly, α1 GlyR-HEK293 cells were split into poly-D-lysine-coated 96-well black Opti-plates (Packard). 16-24 h later, the medium was aspirated, and 100 mL KREBS Buffer [140 mM NaCl/4.7 mM KCl/2.5 mM CaCl$_2$/1.2 mM MgCl$_2$/10 mM HEPES/11 mM D-Glucose, pH 7.4]
20   supplemented with FLIPR® Membrane Potential Assay loading dye and various concentrations of the test compounds was added to the wells. The plate was incubated at 37 °C in a humidified 5% CO$_2$ incubator for 30 min and assayed in a NOVOstar™ (BMG Labtechnologies, Offenburg, Germany) measuring emission at 560
25   nm caused by a 530 nm excitation. Fluorescence measurements were performed immediately before and up to 1 min. after addition of glycine (final concentration 100 mM) to the wells. The experiments were performed in duplicate at least three times for each compound. Percentage inhibition was calculated
30   as: (Response$_{glycine}$-Response$_{test\ cmpd+glycine}$)/Response$_{glycine}$. Inhibition below 20% is characterized as no inhibition (NI).
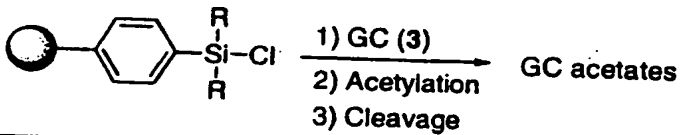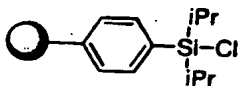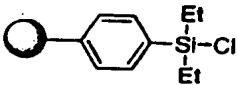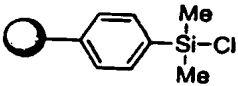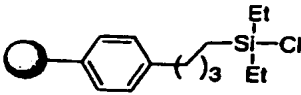
RESULTS

SYNTHESIS

Ginkgolide C (GC, **3**, Figure 1) was chosen as the starting
5 material as it carries the most hydroxyl groups of the
ginkgolides, thus providing possibilities for a more diverse
library. Secondly, GC (**3**), together with GB (**2**), is the most
potent ginkgolide GlyR antagonists (Stromgaard, 2003).

10 **Solid-phase synthesis.** The use of solid-phase synthesis (SPS)
for the preparation of ginkgolide derivatives appeared to be
particularly attractive, as the lack of chromophores renders
them difficult to handle in solution. Moreover, the presence
of multiple hydroxyl groups provides several possibilities of
15 solid-phase attachment. GC (**3**) has four different hydroxyl
groups, three secondary and one tertiary, which exhibit
different reactivities and can therefore be functionalized
selectively. In general, 10-OH is the most reactive for
alkylation and esterification (Corey, 1992). However, acid
20 catalyzed esterification (Jaracz, 2002), as well as reaction
of GC (**3**) with alkyl and aryl sulfonyl halides takes place at
7-OH (Cazaux, 1995; Vogensen, 2003) a selective silylation at
1-OH has also been described (Weingers, 1991).

25 Initially, attempts were made to use a silicon linker, which
could be attached selectively to 1-OH of GC (**3**), followed by
selective derivatizations of 10-OH, 7-OH, and if possible 3-
OH. In a previous example of selective derivatization of 1-OH,
the bulky *tert*-butyldiphenylsilyl was used as a protection
30 group, which however prevented further derivatization at 10-OH
(Weinges, 1991). Hence, it was envisaged that decreasing the
bulk of the silicon linker could allow further derivatization
of 10-OH. Three silicon linkers with variation in the steric
bulk at silicon were synthesized according to known procedures

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(Chan, 1985; Randolph, 1995). Interestingly, isopropyl substituents on the silicon linker as in entry 1 (Table 1) reacted selectively at 1-OH, while decreasing the size of the substituents led to preferential reaction at 7-OH. These
5 linkers, however, were unstable as evidenced by leaching from the resin, and no further studies were pursued.

Table 1. Attachment of GC to silyl resins; mode of attachment.

entry	linker	loading[a] (mmol/g)	mode of attachment[b]
1		0.85	1-OH
2		0.52	1-OH/7-OH (2 : 1)
3		0.35	7-OH
4[c]		1.5	-

10

[a] Loading determined by attachment of Disperse Red, cleavage and spectrophotometric measurements. [b] Mode of attachment determined by acetylation, cleavage and ^{1}H-NMR. spectra of cleaved compounds. Leaching detected with linkers in entries 2 – 4. [c] Prepared from commercial DES resin.

Alternatively, the use of a sulfonyl linkage was studied by anchoring GC (3) through 7-OH, followed by selective derivatization at 10-OH and/or 1-OH and nucleophilic cleavage to provide derivatives of GB (2), and GC (3) with an inverted
5 C-7 configuration. Therefore, a pipsyl moiety was introduced at 7-OH of GC (3) to form 7-O-pipsyl-GC (6) (Scheme 1), which was then attached to a TentaGel-NH₂ resin using Pd-catalyzed carbonylation, similar to that described by Takahashi *et al* (Takahashi, 2001) to give 7 (Scheme 1).
10

Scheme 1
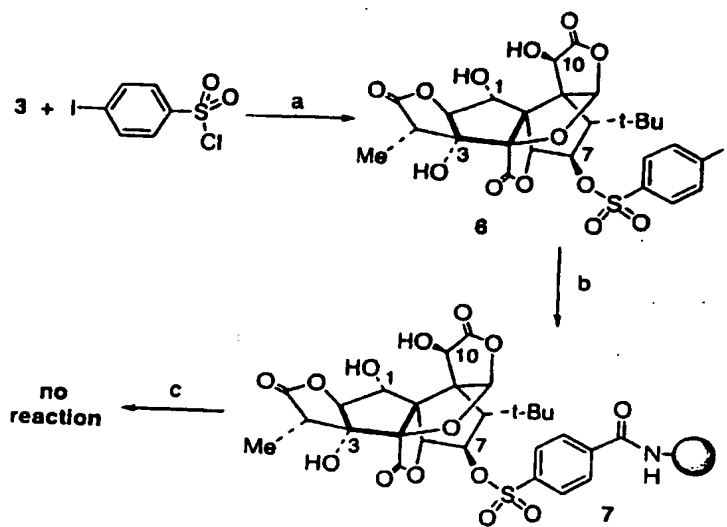
(a) pyridine, CH₂Cl₂; (b) Tentagel-NH₂, CO, Et₃N, Pd(PPh₃)₄,DMF;
(c) TBAH or TBAF, THF

Scheme 1. Attachment of ginkgolide C to solid-phase via sulfonyl linker.

However, treatment of 7 with nucleophiles such as tetrabutyl
15 ammonium fluoride (TBAF) or tetrabutyl ammonium hydride (TBAH) did not release any ginkgolide derivatives. In addition, the solution-phase version of the same displacement of 7-O-pipsyl-GC (6) gave none of the desired products either, thus suggesting that the 7-O-sulfonyl group is not a sufficiently

good leaving group as opposed to a triflate group (Vogensen, 2003). Attachment of GC through 1-OH or 3-OH using other methods did not lead to success probably due to steric hindrance. In addition, substituents at 3-OH readily undergo
5 elimination leading to a thermodynamically favored a,b unsaturated lactone F (Weinges, 1987).

Instead of direct attachment of GC (3) to the solid-phase, attachment via a building block was considered. Ideally, such
10 a building block should function as a multidetachable linker, so that depending on cleavage conditions, ginkgolide derivatives with or without the first building block could be generated. Since GC (3) can be selectively and efficiently benzylated at 10-OH with benzyl bromide under mild conditions
15 in solution (Vogensen, 2003), a benzyl group could serve as the first building block, followed by derivatization of 7-OH, translactonization to form C-6 iso-GC derivatives, removal of 7-OH to reroute into GB derivatives, and if possible functionalize 1-OH and 3-OH, as well. Immobilization of
20 benzyl bromide was investigated in various manners. Initially 4-(bromomethyl)-phenylacetic acid was anchored to the Wang resin and Rink amide resin to give 8 and 9, respectively (Scheme 2). The immobilized benzyl bromides were then reacted with GC (3) to give resins 10 and 11. Cleavage with TFA
25 produced GC derivatives 12 and 13, respectively, which revealed that GC (3) was attached at 10-OH with a high selectivity. The purity of the cleaved products was > 90% as determined by ^{1}H-NMR. Benzyl bromide can also be immobilized to a silicon linker (Plunkett, 1995) representing a traceless
30 linkage, which was also investigated. Resin 14 was synthesized in three steps from bromopolystyrene and 4-(allyldimethylsilyl)benzyl alcohol (Lee, 2001; Iglesias, 2001) followed by reaction with GC (3) to provide resin-bound 10-O-

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benzyl-GC **15** (Scheme 2).   Cleavage with TFA provided **16** in 85%
purity.

Scheme 2
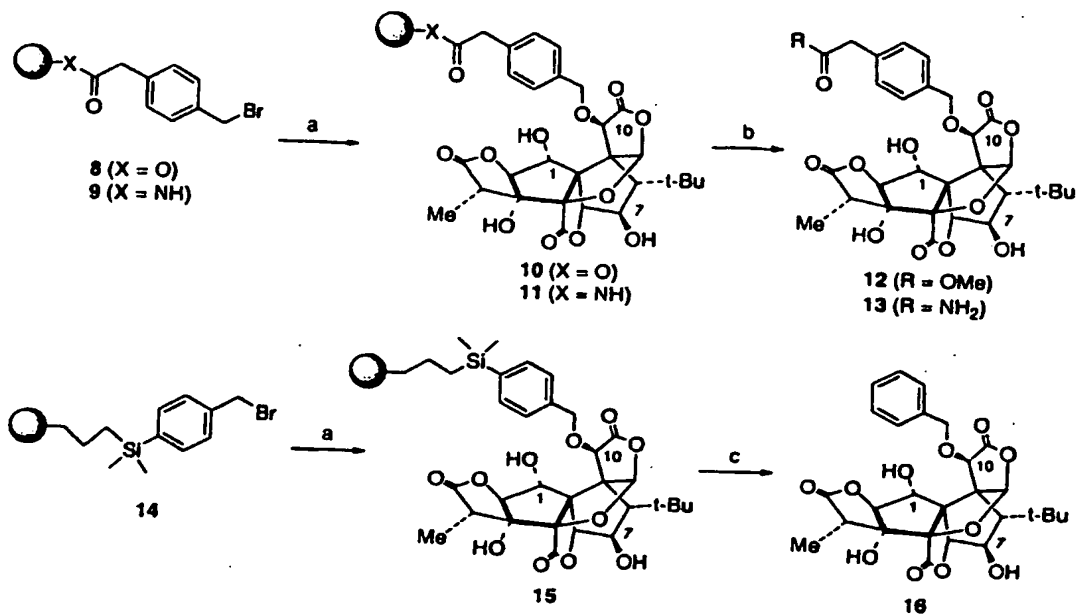
(a) **3**, K$_2$CO$_3$, DMF; (b) Wang resin: i.TFA/CH$_2$Cl$_2$, ii.CH$_2$N$_2$; Rink-amide resin: TFA/H$_2$O; (c) TFA/CH$_2$Cl$_2$
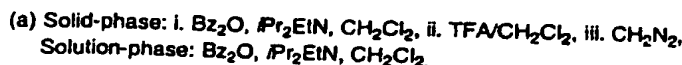
Scheme 2. Attachment of ginkgolide C to a solid-phase via 10-O-benzyl using either Wang resin, Rink amide resin, or traceless silicon linker.

The benzylated Wang resin was selected for further
investigation as it provided sufficiently pure products.
Selective hydroxyl group functionalizations were studied and
compared with similar reactions in solution. Treatment of
resin-bound ginkgolide **10** with benzoic anhydride and Hünig's
base resulted in a mixture of iso-GC benzoates and unreacted
starting material (Scheme 3). On the other hand, solution-
phase reaction of 10-O-benzyl-GC (**16**) under similar conditions
produced iso-GC monobenzoate **17** as the major product.
Acetylation of resin **10** with Ac$_2$O in the presence of Hünig's
base provided iso-GC-bisacetate **18** in a purity of only ca.

60%, while the same reaction in solution provided iso-GC-bisacetate 19 in 90% purity (Figure 2). Similarly, several other reactions on solid-phase such as transformation of GC into GB (Cazaux, 1995; Weinges, 1991) either failed entirely,

5 or proceeded with very low conversion and purity, as compared to the same reaction in solution. It became clear that a solid-phase strategy is not suited for the preparation of a ginkgolide derivative library.

Scheme 3

10

Solid-phase: **10** (R = ⬡OCOCH$_2$)
Solution-phase: **16** (R = H)

(R = CH$_2$COOMe)
17 (R = H)

2-4 : 1

(R = CH$_2$COOMe)
not detected

(a) Solid-phase: i. Bz$_2$O, /Pr$_2$EtN, CH$_2$Cl$_2$, ii. TFA/CH$_2$Cl$_2$, iii. CH$_2$N$_2$,
Solution-phase: Bz$_2$O, /Pr$_2$EtN, CH$_2$Cl$_2$.

Scheme 3. Comparison of ginkgolide C benzoylation using solid-phase or solution-phase chemistry.

15

Solution-Phase Synthesis. Because of the limitations in solid-phase strategy, further derivatizations were performed by solution-phase chemistry. 10-O-benzyl-GC (16) turned out to be a suitable precursor for a wide variety of transformations

20 (Scheme 4). GC-7-benzoate (21) was prepared from 16 by reaction with benzoyl chloride and pyridine in CH$_2$Cl$_2$ in 79% yield. Iso-GC-6-benzoate 17 was efficiently formed (77% yield) by exchanging pyridine with Hünig's base. This remarkable difference in reaction pattern is associated with

25 stabilization of a translactonized anion intermediate by

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hydrogen bonding with 3-OH as reported previously (Jaracz, 2002). Iso-GC-1,6-bisbenzoate **22** was also prepared in 64% yield by further increasing the amount of benzoylation reagent and prolonging the reaction time. Heating of benzoate **17** with
5 Hünig's base in DMF to 100 °C for 1.5 h lead to a remarkable migration of benzoate from C-6 to C-1 with subsequent translactonization of the iso-GC skeleton back to the GC skeleton to form **23** (78% yield, Scheme 4). The driving force for this rearrangement is the greater thermodynamic stability
10 of the original ginkgolide core. Namely, the bulky tert-butyl group is axial in iso-GC while it is pseudo-equatorial in GC and the 6-membered ring E in iso-GC adopts a boat conformation.

Scheme 4
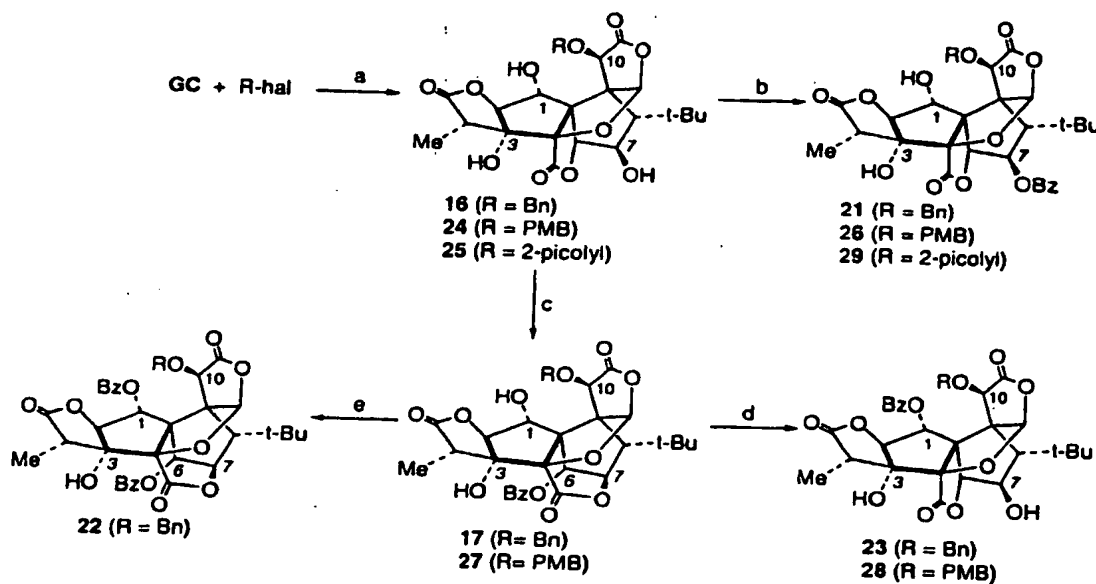
(a) K_2CO_3, DMF; (b) BzCl (3 eq.), pyridine, CH_2Cl_2; (c) Bz_2O (3 eq.), iPr_2EtN, CH_2Cl_2;
15 (d) iPr_2EtN, DMF, 100°C; (e) Bz_2O (6 eq.), iPr_2EtN, CH_2Cl_2

Scheme 4. Synthesis of ginkgolide C benzoates. PMB = p-methoxybenzyl.

According to previously established methods[23,43] 10-(4-methoxy-benzyloxy)-GC (**24**) and 10-(2-pyridinyl-methoxy)-GC (**25**) were prepared from GC in 94% and 97% yields, respectively (Scheme 4). Benzoate derivatives **26, 27, 28** and **29** were prepared from

5 **24** and **25** using the same conditions as described above for **16** (Scheme 4). The ester derivatives prepared from **24** were consequently subjected to oxidative removal of the *p*-methoxybenzyl (PMB) group by cerium(IV) ammonium nitrate (CAN) to obtain derivatives **30, 31** and **32** (60-81% yield, Figure 3).

10 Milder oxidation reagents, such as dichlorodicyano quinone (DDQ) did not cleave the PMB group.

Introduction of carbamate moieties into the various hydroxyl groups of ginkgolides was next investigated since such

15 derivatives would yield important information for SAR studies. Carbamates at C-7 were efficiently prepared from **16** in two steps (Scheme 5) by reaction with *p*-nitrophenylchloroformate and pyridine in CH_2Cl_2 to form **33** in 61% yield; carbonate **33** was further reacted with various aliphatic amines in THF to

20 yield carbamates **34 - 37** (81-92% yield, Table 2).

Scheme 5

16 (R = Bn)
24 (R = PMB)

33 (R = Bn)
43 (R = PMB)

34 - 37 (R = Bn)
44 - 47 (R = PMB)
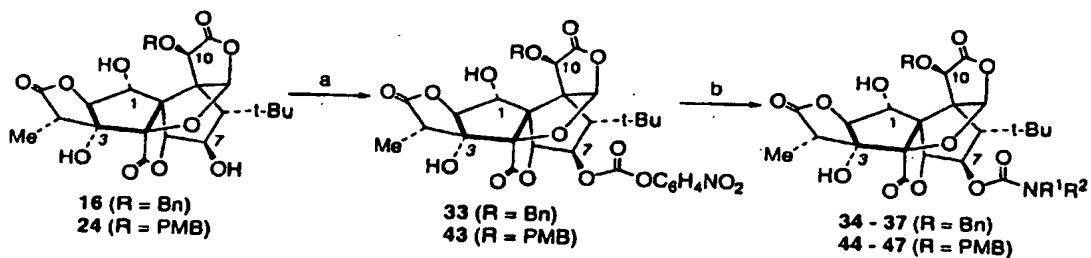
(a) $ClCOOC_6H_4NO_2$, pyridine, CH_2Cl_2; (b) NHR^1R^2, THF

Scheme 5. Synthesis of C-7 carbamates from 10-alkyl substituted GC. PMB = *p*-methoxybenzyl.

25

Again, a remarkable difference was observed when Hünig's base was used instead of pyridine (Scheme 6).

Scheme 6
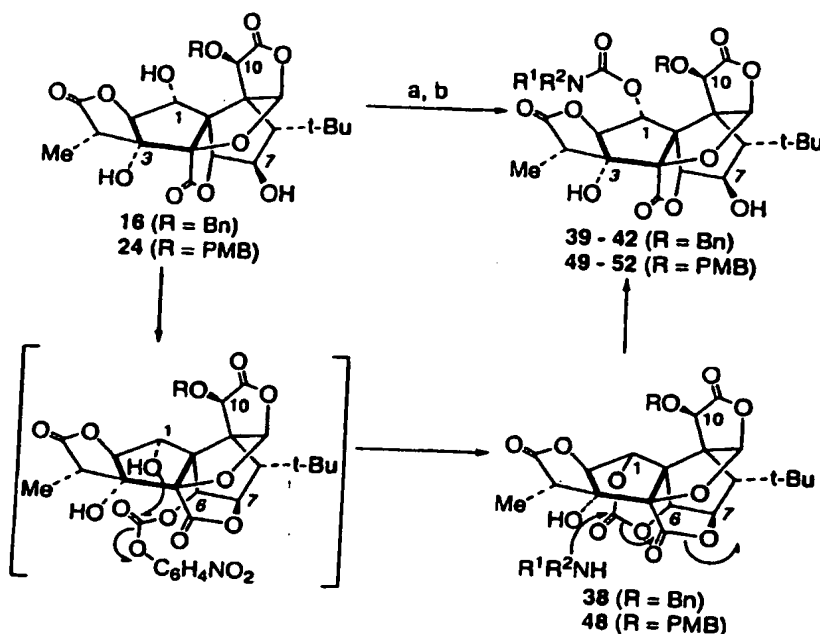
(a) ClCOOC$_6$H$_4$NO$_2$, iPrEt$_2$N, CH$_2$Cl$_2$; (b) NHR^{1}R^2, CH$_2$Cl$_2$/THF

Scheme 6. Synthesis of C-1 carbamates from 10-alkyl substituted GC, showing migratory mechanism. PMB = p-methoxybenzyl.

It is plausible that a highly reactive iso-GC 6-(p-nitrophenyl)carbonate is formed first, which reacts further with 1-OH as in the case of the migration of benzoate in **23**. The product of this reaction, however, is cyclic carbonate **38** with a bridge between C-1 and C-6. This compound is unstable and hydrolyzes easily even on silica gel to form **16**. Treatment of **38** with various aliphatic amines in THF provided facile opening of the carbonate bridge to form carbamates at C-1 with consequent translactonization of ring E into the

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native form, 39 - 42. Even bulky amines such as tert-
butylamine reacted to completion in both cases forming 35 and
40, i.e., ginkgolides with two tert-butyl groups. All three
reactions are performed in one pot to obtain the desired C-1
5   products in 50-78% yield from 16 after a single chromatography
(Table 2). The corresponding sets of carbamates 44 - 47 (C-7)
and 49 - 52 (C-1) were prepared from 24 (Schemes 5 and 6,
Table 2), while removal of the PMB group afforded the
nonaromatic ginkgolide carbamates 53 - 60 (Table 3).
10

BIOLOGICAL ACTIVITY

The ginkgolide derivatives were investigated for their
abilities to antagonize glycine-induced responses from
homomeric a1 GlyRs. In brief, homomeric a1 GlyR was stably
15   expressed in HEK293 cells and a fluorescence-based membrane-
potential kit was used to detect receptor activity.[53] The
decrease in glycine response was measured by pre-incubation of
the test compound prior to addition of 100 mM glycine. GC (3)
was used as the reference compound. At a concentration of 10
20   mM GC (3) the response induced by glycine was inhibited by
97%. Due to the relatively low potency of all derivatives,
they were investigated at a concentration of 100 mM for
determination of the %-inhibition (Tables 2-5). However, none
of the ginkgolide derivatives tested were more potent than the
25   parent compound GC (3), and it follows that any modification
of the hydroxyl groups leads to a significant decrease in
biological activity. Thus, in the discussion below it should
be noted that the relative differences between these
derivatives are only minor since all compounds are only weak
30   antagonists of the GlyR.

Table 2. Chemical yields and biological activities of C-7 and C-1 carbamates of 10-alkyl-GC.
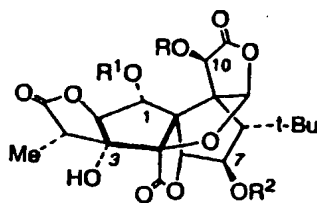
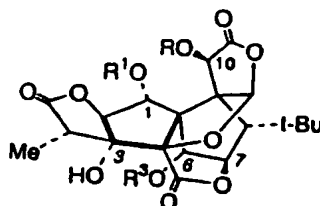| compound	R	R[1]	R[2]	yield (%)	% inhibition[a]
34	Bn	H	CONHMe	88[b]	NI
35	Bn	H	CONHtBu	88[b]	29
36	Bn	H	$CONC_4H_8O$	92[b]	NI
37	Bn	H	$CONC_5H_{10}$	81[b]	NI
39	Bn	CONHMe	H	64[c]	NI
40	Bn	CONHtBu	H	59[c]	42
41	Bn	$CONC_4H_8O$	H	78[c]	NI
42	Bn	$CONC_5H_{10}$	H	50[c]	31
44	PMB	H	CONHMe	74[d]	NI
45	PMB	H	CONHtBu	77[d]	39
46	PMB	H	$CONC_4H_8O$	90[d]	NI
47	PMB	H	$CONC_5H_{10}$	86[d]	29
49	PMB	CONHMe	H	67[e]	NI
50	PMB	CONHtBu	H	60[e]	33
51	PMB	$CONC_4H_8O$	H	75[e]	NI
52	PMB	$CONC_5H_{10}$	H	53[e]	NI

[a] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; %-inhibition was calculated as: $(Response_{glycine}-Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate. [b] from 33. [c] from 16. [d] from 43. [e] from 24. NI = no inhibition, i.e., inhibition below 20%. PMB = p-methoxybenzyl.

Ginkgolide derivatives with carbamates in position 1 or 7, and a benzyl or PMB group in the 10-position were either inactive at the concentrations tested, or only moderately active (Table 2).   Interestingly, all derivatives with moderate activity

5   contained a *tert*-butyl carbamate, and the presence of this group, rather than the position seems to be of importance for biological activity in this set of derivatives tested. For the corresponding carbamates without the benzyl or PMB group it appears as if both the position and the nature of the

10   substituent are of importance (Table 3): Compounds 57 and 58 show a ca. 70% inhibition of the glycine responses, whereas other derivatives are either inactive or only moderately active.   It is interesting to compare the activities of 57 with those of 39 and 49, the only difference being the benzyl

15   substitution at 10-OH, thus indicating that the latter is detrimental for activity at GlyRs. Moreover, the activities of 57 and 58 compared to those of 53 and 54 show that substitution at 1-OH is preferred over 7-OH, while comparison with 59 and 60 indicates that there might be limitation to the

20   size of the substituent that is tolerated.

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Table 3. Chemical yields and biological activities of C-7 and C-1 carbamates of ginkgolide C.
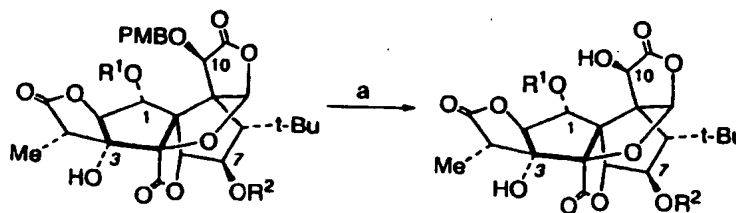
compound	R^1	R^2	yield (%)	% inhibition[b]
53	H	CONHMe	69	NI
54	H	CONHtBu	80	NI
55	H	$CONC_4H_8O$	60	44
56	H	$CONC_5H_{10}$	64	34
57	CONHMe	H	86	76
58	CONHtBu	H	84	71
59	$CONC_4H_8O$	H	80	NI
60	$CONC_5H_{10}$	H	79	33

a $(NH_4)_2Ce(NO_3)_6$, $MeCN/H_2O/CHCl_3$. PMB = p-methoxybenzyl

a Inhibition of 100 µM glycine-induced response by 100 µM of test compound; %-inhibition was calculated as: $(Response_{glycine}-Response_{test\ cmpd+glycine})/Response_{glycine}$. Values are means of three independent experiments performed in duplicate. NI = no inhibition, i.e., inhibition below 20%. PMB = p-methoxybenzyl.

The benzylated or benzoylated derivatives in Table 4 show a certain degree of variation in activities. The most potent derivatives are those with only one benzyl substituent in 10-OH, such as compounds **16**, **24** and **25**, and particularly **25** with a 2-picolyl substituent exhibits a 75% inhibition. Addition of benzoyl groups do not improve activity, while the presence of only one benzoyl group, such as **30** and **32** leads to a complete loss in activity (Table 4).

Table 4. Biological activities of ginkgolide derivatives.
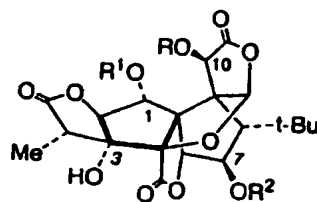
compound	R	R^1	R^2	% inhibition[a]
12	MeO$_2$CCH$_2$C$_6$H$_4$CH$_2$	H	H	NT
13	NH$_2$COCH$_2$C$_6$H$_4$CH$_2$	H	H	NT
16	Bn	H	H	59
21	Bn	H	Bz	45
23	Bn	Bz	H	60
24	PMB	H	H	52
25	2-picolyl	H	H	75
26	PMB	H	Bz	35
28	PMB	Bz	H	NI
29	2-picolyl	H	Bz	51
30	H	H	Bz	NI
32	H	Bz	H	NI

[a] Inhibition of 100 μM glycine-induced response by 100 μM of test compound; %-inhibition was calculated as: (Response$_{glycine}$-Response$_{test\ cmpd+glycine}$)/Response$_{glycine}$. Values are means of three independent experiments performed in duplicate. NT = not tested. NI = no inhibition, i.e., inhibition below 20%. PMB = *p*-methoxybenzyl.

Finally a range of iso-ginkgolide derivatives were investigated, with some of them showing reasonable potencies (Table 5). Particularly compound 17, with a 90% inhibition in glycine responses is the most potent of the 43 derivatives, although still considerably less potent than GC (3), a 30 uM concentration of 17 giving only a 39% inhibition. However,

rearrangement of the ginkgolide skeleton, as in the iso-ginkgolide derivatives, seems to be an acceptable modification for GlyR inhibition.

5

Table 5. Biological activities of iso-ginkgolide derivatives.

compound	R	R^I	R^J	% inhibition[a]
17	Bn	H	Bz	90
18	$MeO_2CCH_2C_6H_4CH_2$	Ac	Ac	NT
19	Bn	Ac	Ac	21
20	PMB	Ac	Ac	36
22	Bn	Bz	Bz	42
27	PMB	H	Bz	49
31	H	H	Bz	63

[a] Inhibition of response induced by 100 µM glycine by 100 µM test compound; %-inhibition was calculated as: ($Response_{glycine}$ - $Response_{test\ cmpd+glycine}$)/$Response_{glycine}$. Values are means of three independent experiments performed in duplicate. NT = not tested. PMB = p-methoxybenzyl.

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DISCUSSION

We have shown that the solid-phase reactions of ginkgolides
15 differ from those in solution; particularly, selectivity is greatly diminished. Although the preparation of linear peptides, oligosaccharides and nucleotides are performed routinely by the solid-phase method, the branched sugar analogs have to be prepared in solution using extensive

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protection/deprotection strategy (Plante, 2001; Tanaka, 2002; Ning, 2002). We have shown that ginkgolide C in solution can be selectively transformed into various derivatives via rearrangement and migration. Since hydroxyl groups that are

5   unchanged in the product, e.g. 3-OH and 7-OH, participate during the reaction process their protection would presumably hamper the entire process. Thus the role of 7-OH in reactions described here is fundamental.

10   The synthesized ginkgolide derivatives were investigated as GlyR antagonists. using a high-throughput assay, hence providing the first SAR study of ginkgolides and GlyR. In general, the ginkgolide derivatives prepared were less potent than the parent compound, GC (3) and in many cases the

15   derivatives were totally devoid of activity. These results indicate that substitutions of the hydroxyl groups in ginkgolides are not beneficial for antagonistic activity at GlyR, and clearly other means of improving the activity of the parent compounds will be required in the future. In addition,

20   these results show that the structure-activity relationships differ significantly from those observed with PAFR, as best exemplified by the iso-ginkgolide derivatives. When tested against PAFR, iso-GC acetates were devoid of activity;[41] however, in the present studies, although much less potent

25   than the parent GC 3, the iso-ginkgolide derivative 17 was the most potent of the compounds tested.

Previous studies have indicated that ginkgolides might antagonize GlyRs by binding to an intra-ion channel site

30   (Stromgaard, 2002; Stromgaard, 2003), thus acting as a plug in the ion channel of the GlyR. Moreover, it was suggested that the conformation of the ginkgolide was very important for antagonistic activity (Stromgaard, 2002). This study has shown

that any modification of the hydroxyl groups leads to a significant loss in activity, which could be attributed to a change in the overall structure of the ginkgolides or by a reduction in the hydrogen bonding capacity of the hydroxyl

5   groups. Further studies are needed to elucidate the binding of ginkgolides to the GlyRs.

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What is claimed is:

`1. A compound having the structure:

wherein R is H or -A-Ar,

where A is an alkyl group; and

Ar is an aryl group, which may contain heteroatoms and may be unsubstituted or substituted by one to five substituents each selected from the group consisting of hydrogen, alkoxy, $-CH_2CO_2R^4$, and $-CH_2CONR^5R^6$;

where R^4 is an alkyl group; and

R^5 and R^6 are each, independently, hydrogen or a branched or unbranched alkyl group;

wherein R^1 is H or $-COR^7$,

where R^7 is alkyl, aryl or amino;

wherein R^2 is present or absent, and when present is H, $-COR^8$ or $-CO-Z-R^8$;

where R^8 is alkyl, aryl or amino; and

Z is oxygen;

wherein R³ is present or absent, and when present is –COR⁹;
where R⁹ is alkyl or aryl;

wherein only one of R² or R³ is present in the compound;

wherein only two of R, R¹, R² and R³ are H; and

wherein each of a and b designates a single covalent bond which is present or absent,
where bond a is present when R³ is absent and bond b is present when R² is absent;

or an optically pure enantiomer or a pharmaceutically acceptable salt of the compound.

2. The compound of claim 1, having the structure
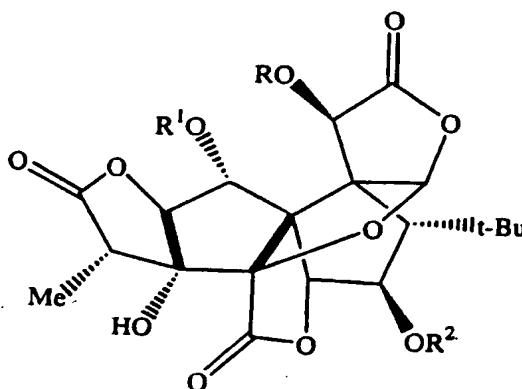
wherein R, R¹, and R² are as defined in claim 1.

3. The compound of claim 1, having the structure
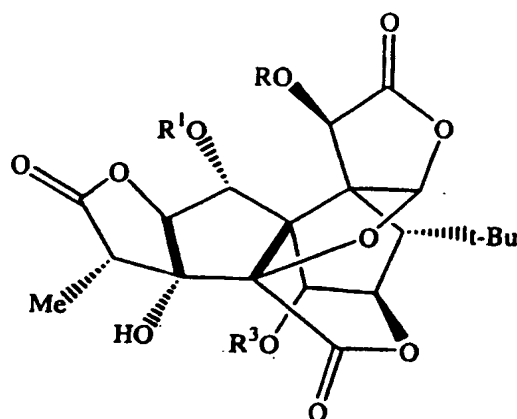
wherein R, R¹, and R³ are as defined in claim 1.

4. The compound of claim 2,
    wherein R is H or -A-Ar-;
        where A is $-CH_2-$,
        Ar is a phenyl group or a picolyl group, either of which may be substituted or unsubstituted by a substituent selected from the group consisting of hydrogen, methoxy, $-CH_2CO_2Me$, and $-CH_2CONH_2$.

5. The compound of claim 4,
    wherein R is H, benzyl, para-methoxybenzyl or picolyl.

6. The compound of claim 2,
    wherein R¹ is H or $-COR^7$;
        where R^7 is methyl, phenyl or $-NR^5R^6$;
        where R^5 and R^6 are each, independently, hydrogen, methyl, or t-butyl, or wherein R^5 and R^6 together with the nitrogen to which they are attached form a morpholine or piperidine.

7. The compound of claim 6,

wherein R^1 is H, benzoyl, -COMe, -CONHMe, -CONHtBu, piperidyl, or morpholinyl.

8. The compound of claim 2,

wherein R^2 is H, -COR^8 or CO-Z-R^8;

where R^8 is -NR^{5}R^6 or phenyl, which may be unsubstituted or substituted by one to five substituents which are each, independently, halogen or -NO$_2$.

where R^5 and R^6 are each, independently, hydrogen, methyl, or t-butyl, or wherein R^5 and R^6 together with the nitrogen to which they are attached together form a morpholine or piperidine.

9. The compound of claim 8,

wherein R^2 is H, benzoyl, -COMe, -CO$_2$C$_6$H$_4$NO$_2$, -CONHMe, -CONHtBu, piperidyl or morpholinyl.

10. The compound of claim 3,

wherein R is H or -A-Ar-;

where A is -CH$_2$-,

Ar is a phenyl group or a picolyl group, either of which may be substituted or unsubstituted by a substituent selected from the group consisting of hydrogen, methoxy, -CH$_2$CO$_2$Me, and -CH$_2$CONH$_2$.

11. The compound of claim 10,

wherein R is H, benzyl, p-methoxybenzyl or picolyl.

12. The compound of claim 3,

wherein R^1 is H or -COR^7,

where R^7 is methyl, phenyl or $-NR^5R^6$;

where R^5 and R^6 are each, independently, hydrogen, methyl, or t-butyl, or wherein R^5 and R^6 together with the nitrogen to which they are attached together form a morpholine or piperidine.

13. The compound of claim 12, wherein R^1 is H, phenyl, -COMe, -CONHMe, -CONHtBu, -CONC$_5$H$_{10}$ or CONC$_4$H$_8$O.

14. The compound of claim 3, wherein R^3 is benzoyl, -COMe or -CO$_2$C$_6$H$_4$NO$_2$.

15. The compound of claim 1, having the formula
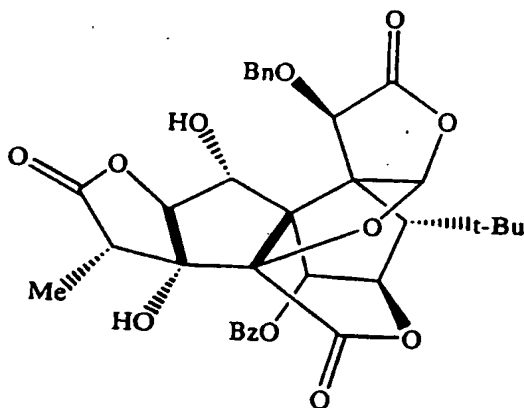
16. The compound of claim 1, having the structure
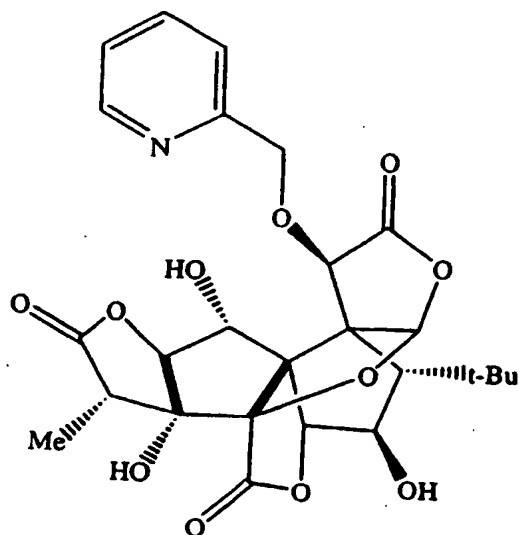
17. The compound of claim 1, having the structure
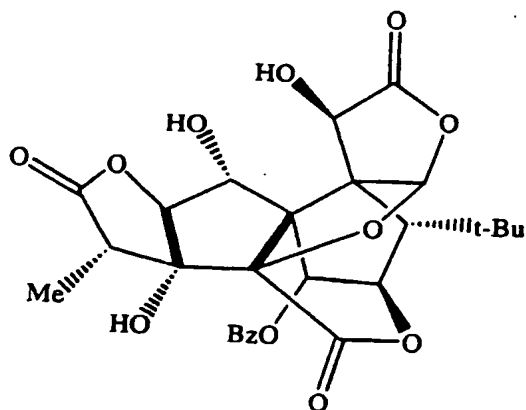
18. The compound of claim 1, having the structure
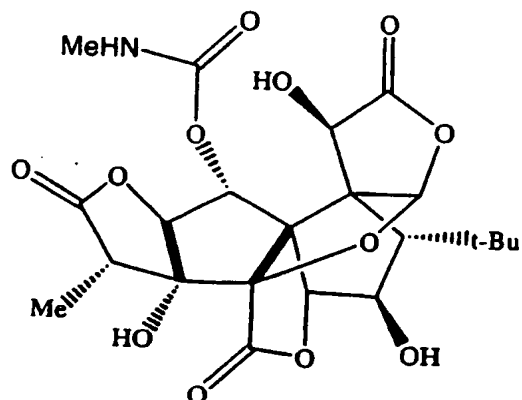
19. The compound of claim 1, having the structure
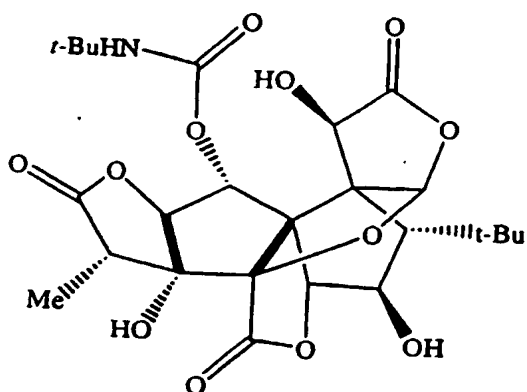
20. The compound of claim 1, having the structure
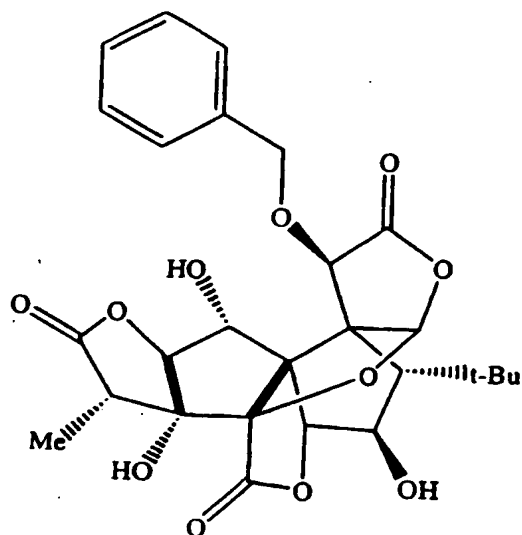
21. The compound of claim 1, having the structure
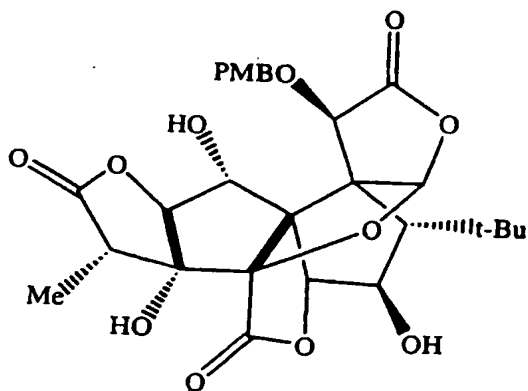
22. A method of inhibiting the activity of a glycine receptor comprising contacting the glycine receptor with the compound of any one of claims 1 - 21.

23. The method of claim 22 wherein the compound is
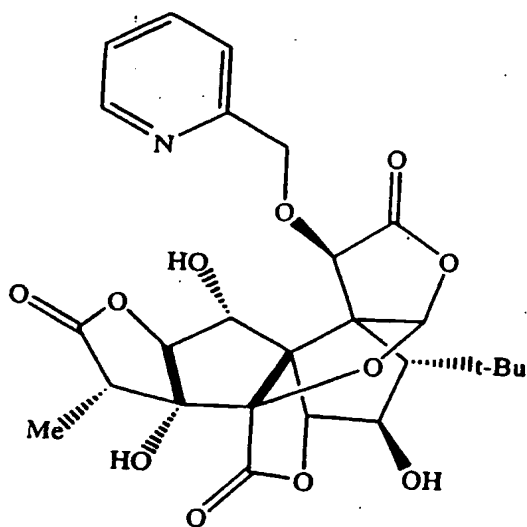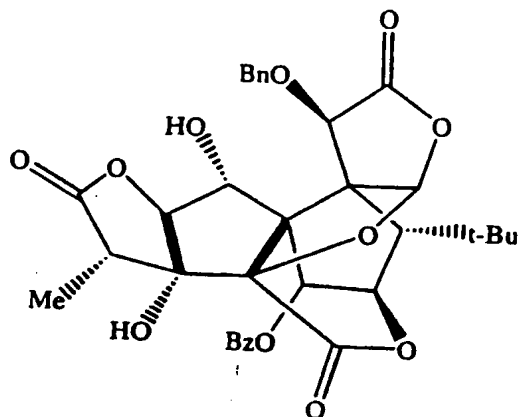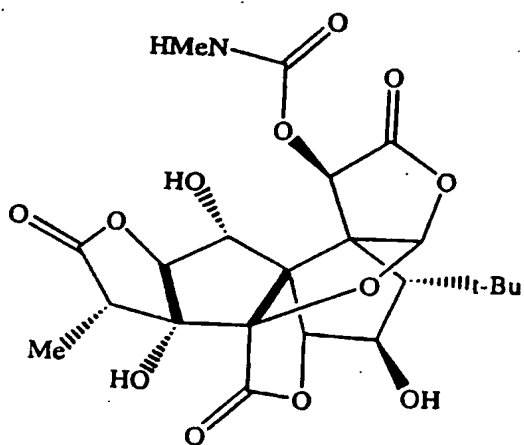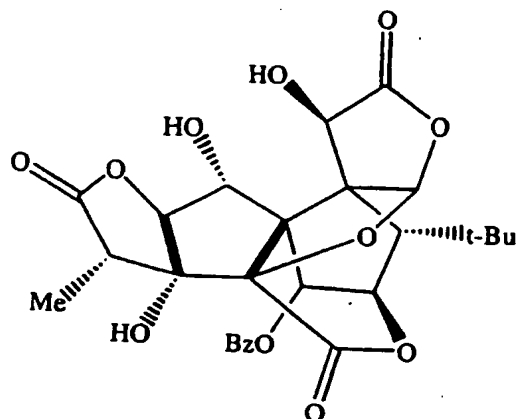
, or
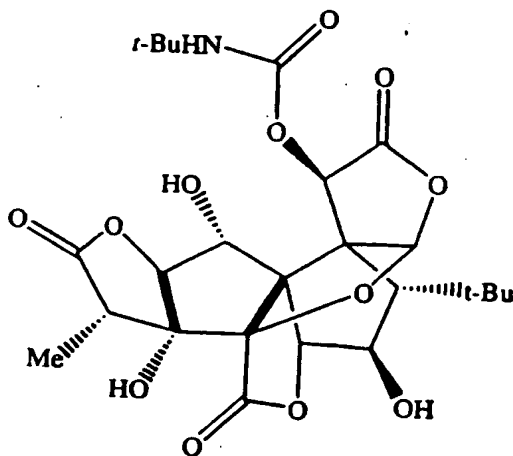
24. A method of treating Alzheimer's disease in a subject in need of such treatment, comprising administering to the subject the compound of claim 15, 16, 17, 18 or 19.

25. A pharmaceutical composition comprising the compound of claim 15, 16, 17, 18 or 19 and a pharmaceutical carrier.

26. A process of preparing the compound of claim 1, comprising the step of reacting a compound having the structure
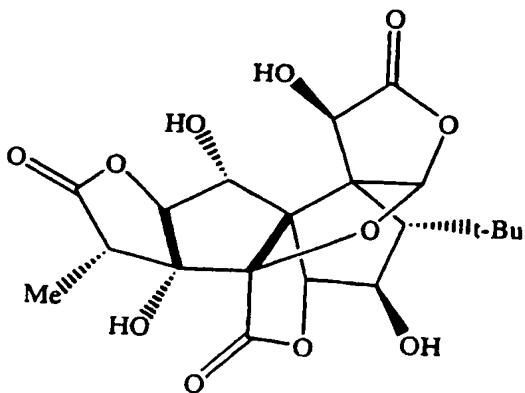
with an electrophile to form the compound.

27. A process of preparing the compound of claim 2, comprising the steps of:
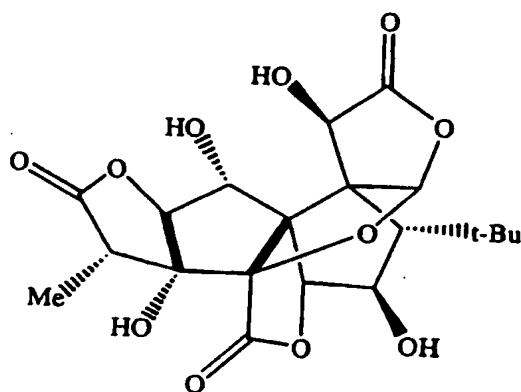
i) reacting a compound having the structure

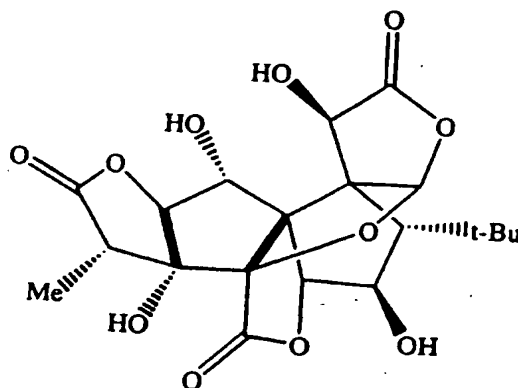with either 4-methoxybenzyl chloride or benzyl chloride, and a suitable base to form a compound having the structure
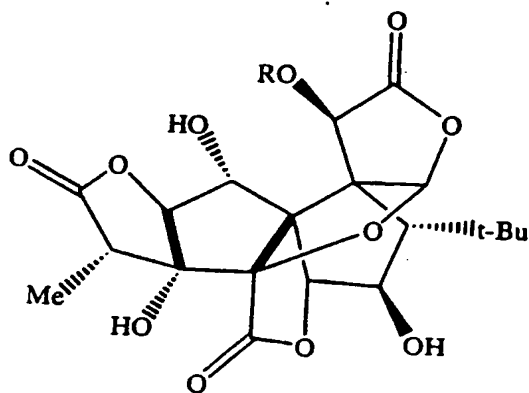
wherein R is benzyl or *p*-methoxybenzyl; and

ii) reacting the product of step i) with an electrophilic reagents to form the compound of claim 2.

28. A process of preparing the compound of claim 3, comprising the steps of:
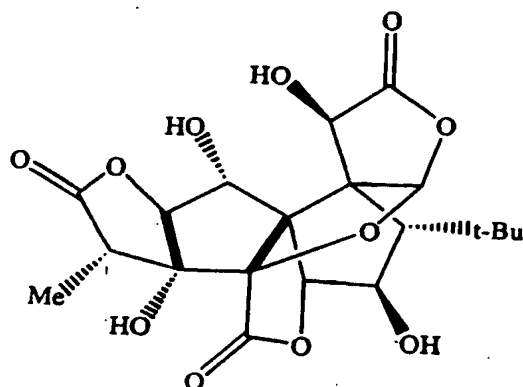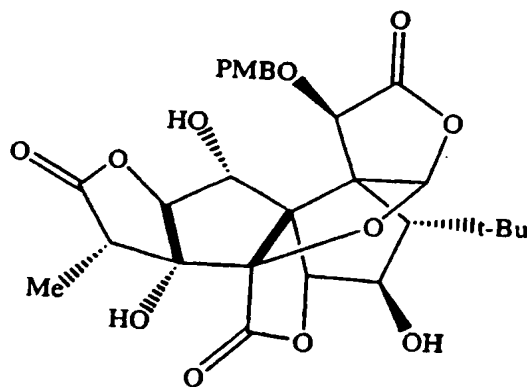
i) reacting a compound having the structure

with 4-methoxybenzyl chloride or benzyl chloride, and a suitable base to form a compound having the structure

wherein R is benzyl or p-methoxybenzyl; and

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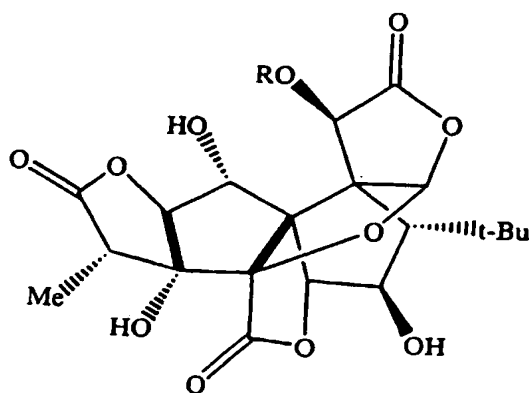
ii) reacting the product of step i with the appropriate electrophilic reagents to form the compound of claim 3.

29. A process of preparing the compound of claim 15, comprising the steps of:
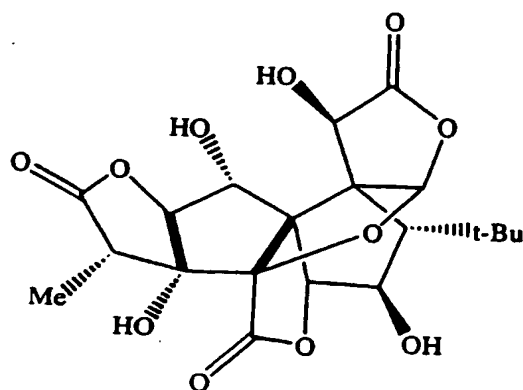
i) reacting a compound having the structure

in dimethylformamide with a resin and an appropriate base to form a compound having the structure

ii) cleaving the product of step i) from the resin by mixing the product of step i) with trifluoracetic acid in a polar solvent to form a compound having the structure

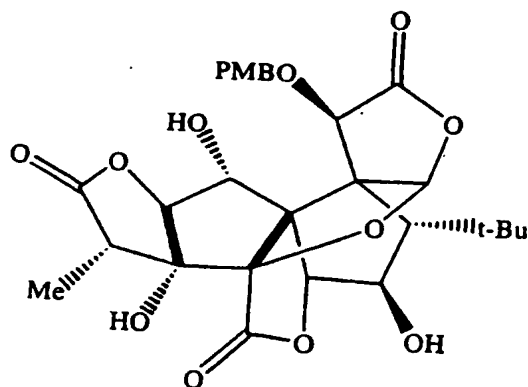wherein R^{10} is -H, $-CH_2CO_2H$ or CH_2CONH_2; and

-117-
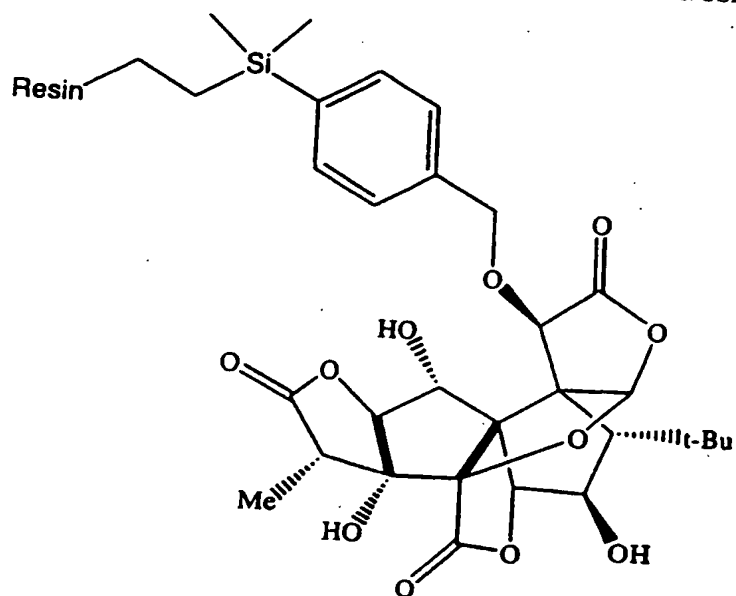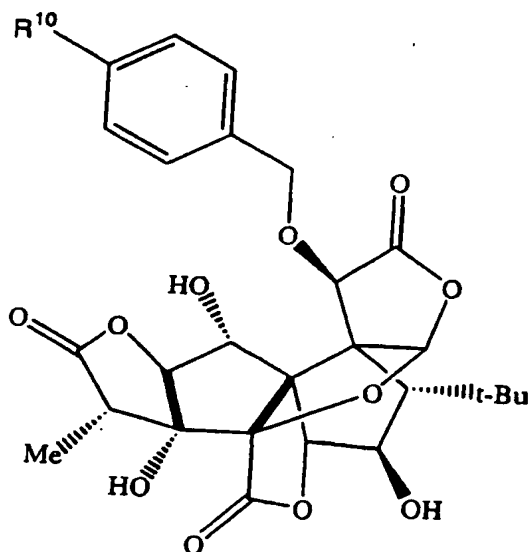
iii) dissolving the product of step ii) and a suitable amine base in an appropriate solvent and reacting with benzoic anhydride, thereby forming the compound of claim 15.

30. A process of preparing the compound of claim 16, comprising the step of reacting a compound having the structure
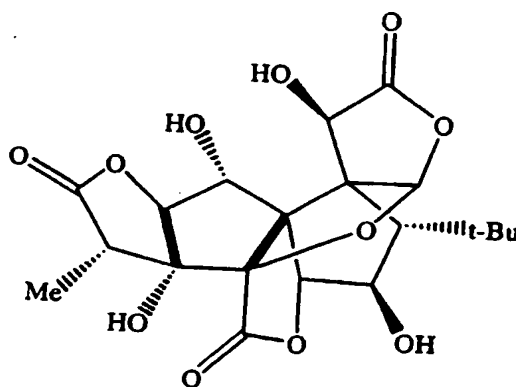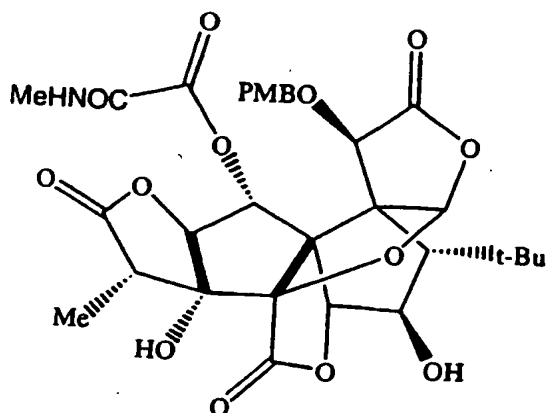

with 2-picolyl chloride in a polar solvent with a suitable base, thereby forming the compound of claim 16.

31. A process of preparing the compound of claim 17, comprising the steps of:

i) reacting a compound having the structure

with 4-methoxybenzyl chloride in a polar solvent with a suitable base, providing a compound having the structure

; and

ii) dissolving the product of step i) and a suitable amine base in a polar solvent and reacting with benzoic anhydride, thereby forming the compound of claim 17.

32. A process of preparing the compound of claim 18, comprising the steps of:
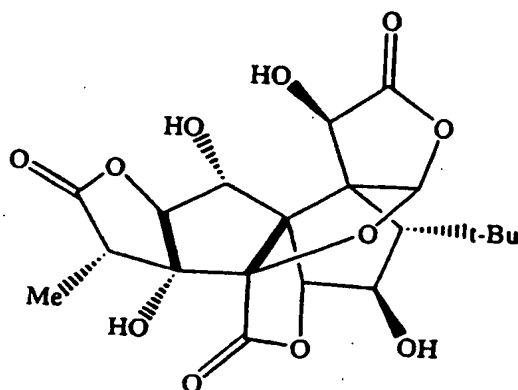
i) reacting a compound having the structure

with 4-methoxybenzyl chloride in an appropriate polar solvent with a suitable base, providing a compound having the structure

; and

ii) dissolving the product of step i) and iPr₂EtN base in a suitable solvent and reacting with p-nitrophenyl chloroformate and then with MeNH₂, forming a compound having the structure
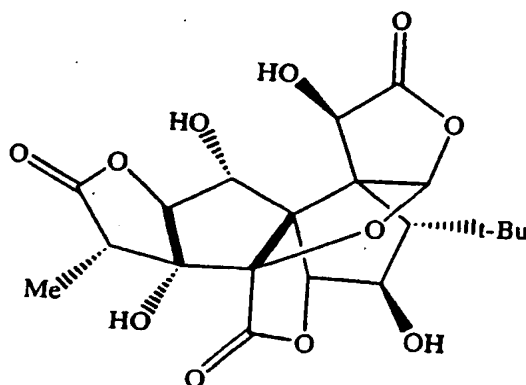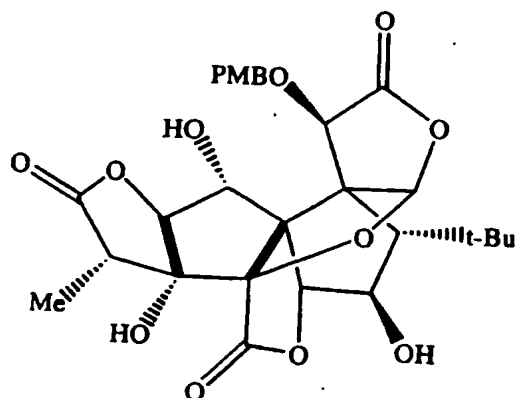
-120-

; and

iii) dissolving the product of step ii) in a suitable solvent and reacting with $(NH_4)_2Ce(NO_3)_6$, thereby forming the compound of claim 18.

34. A process of preparing the compound of claim 19, comprising the steps of:
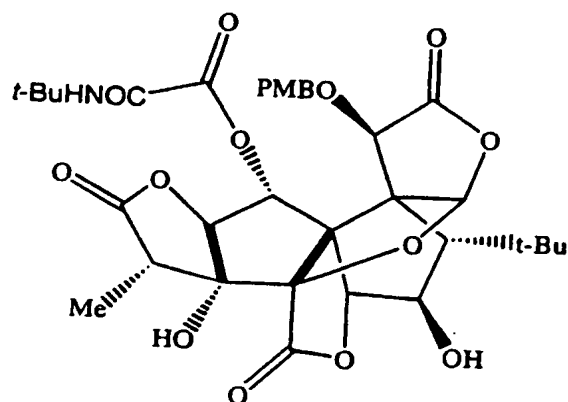
i) reacting a compound having the structure

with 4-methoxybenzyl chloride in an a polar solvent with a suitable base, providing a compound having the structure
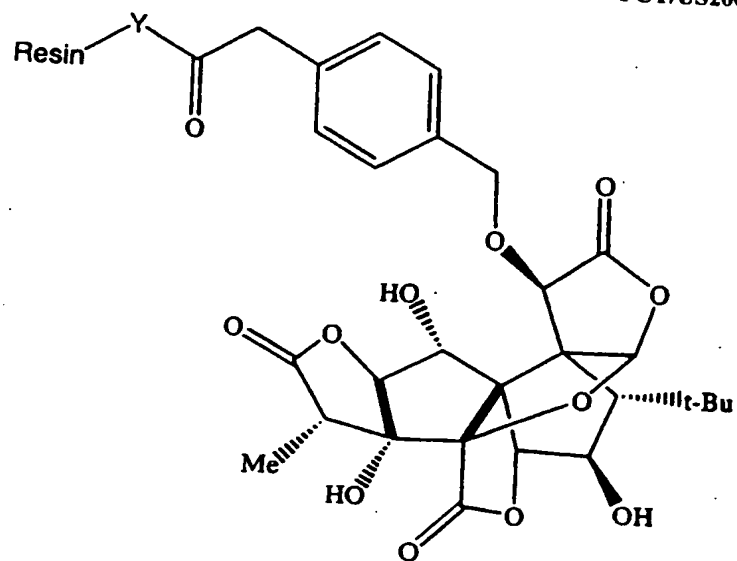
; and

ii) dissolving the product of step i) and *i*Pr₂EtN base in a suitable solvent and reacting with *p*-nitrophenyl chloroformate and then with *t*BuNH₂, thereby forming the product
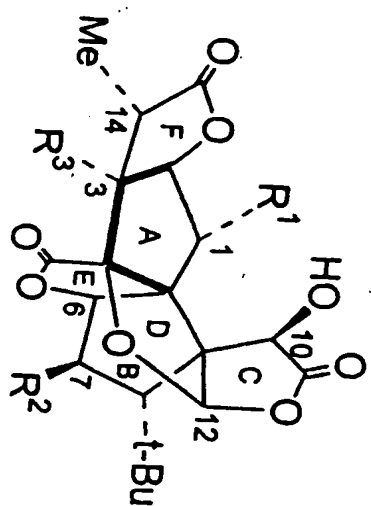

; and

iii) dissolving the product of step ii) in a suitable solvent and reacting with $(NH_4)_2Ce(NO_3)_6$, thereby forming the compound of claim 19.

35. A compound having the formula

wherein Y is oxygen or -NH-.

FIGURE 1

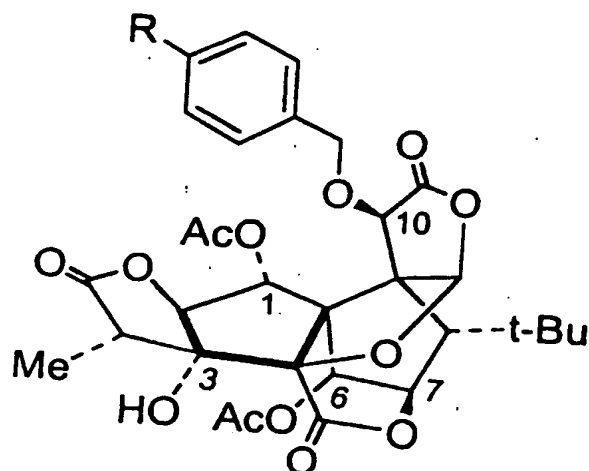Ginkgolides A, B, C, J, and M.

	R^1	R^2	R^3
Ginkgolide A (GA, **1**)	H	H	OH
Ginkgolide B (GB, **2**)	OH	H	OH
Ginkgolide C (GC, **3**)	OH	OH	OH
Ginkgolide J (GJ, **4**)	OH	OH	OH
Ginkgolide M (GM, **5**)	OH	OH	H

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FIGURE 2

10-Alkyl-iso-GC-1,6-bisacetates

18 (R= CH$_2$COOMe)
19 (R = H)
20 (R = OMe)

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FIGURE 3

Benzoates of ginkgolide C.